(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 December 2003 (11.12.2003)

PCT

(10) International Publication Number
WO 03/101963 A1

(51) International Patent Classification[7]: C07D 211/14, A61K 31/445, A61P 3/00

(21) International Application Number: PCT/US03/14540

(22) International Filing Date: 22 May 2003 (22.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/384,603 30 May 2002 (30.05.2002) US

(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MITCH, Charles, Howard** [US/US]; 3210 Grove Parkway, Columbus, IN 47203 (US). **QUIMBY, Steven, James** [US/US]; 10657 Kestrel Court, Noblesville, IN 46060 (US).

(74) Agents: **GINAH, Francis, O.** et al.; Eli Lilly And Company, P. O. Box 6288, Indianapolis, IN 46206-6288 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

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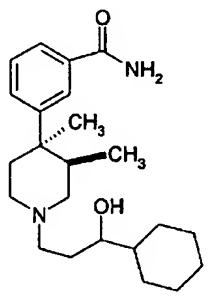
(54) Title: OPIOID RECEPTOR ANTAGONISTS



(I)

(57) Abstract: A compound of the formula (I) : or a pharmaceutically acceptable salt, enantiomer, racemate, diastereomers or mixtures thereof, or a solvate thereof, formulations and methods of use thereof are disclosed.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Opioid Receptor Antagonists

The present invention is in the field of medicinal chemistry. The invention relates specifically to compounds useful as opioid antagonists, methods of treatment, methods of using, and pharmaceutical compositions thereof.

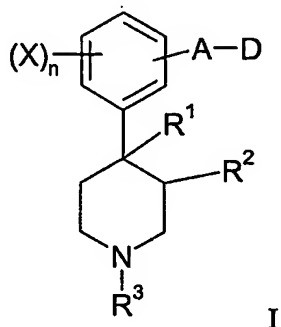
Background:

Three types of opioid receptors, mu, kappa, and delta opioid receptors are generally reported. Recent evidence points to the interactions between receptor dimer combinations of mu, kappa and/or delta receptors (called heterodimers) as also contributing to opioid activity. Opiate receptors and their normal regulation or lack thereof, has been implicated in disease states including irritable bowel syndrome, nausea, vomiting, pruritic dermatoses, depression, smoking and alcohol addiction, sexual dysfunction, stroke and trauma in animals. Therefore it is not surprising that the ability to antagonistically bind opioid receptors has been shown to produce ameliorative, preventative and/or treatment effects in animals including humans afflicted with one or more of these disease states.

More recently, antagonists of the opioid receptors have been found to increase metabolic energy consumption, and reduction of weight in obese rats while maintaining muscle mass. These findings indicate that an effective opioid antagonist may be useful in preventing, treating and or ameliorating the effect of obesity. Considering the percentage of the population that is obese in Western societies and the indirect costs associated with treating the effects and symptoms of obesity and Related Diseases, the impact of these findings cannot be overstated.

Though many opioid antagonists have been disclosed, the search continues for alternative and/or improved or more effective antagonists having an overall benefit to the patient with little or no major side effects. U.S Patent No. 4,891,379 discloses phenylpiperidine opioid antagonists useful for the treatment of diabetes and obesity. Clinical development of a compound claimed in U.S. Patent No. 4,191,771 was discontinued due to poor bioavalibility characteristics. Bicyclic analogs of phenyl piperidine have been prepared and reported as opioid antagonists by Wentland, et al., Biorganic and Medicinal Chemistry Letters 11 (2001) 623-626; see also Wentland, et al., Biorganic and Medicinal Chemistry Letters 11 (2001) 1717-1721. Finally, European

Patent application number 1 072592A2 filed May 18, 2000, discloses phenylpiperidine compounds of formula I



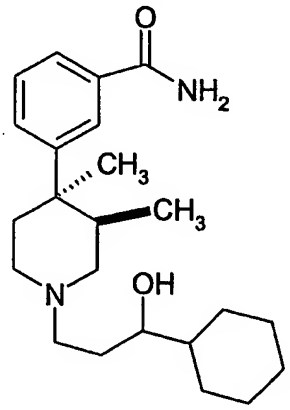
I

wherein A, D, R^1, R^2, R^3 X, and n have meanings given in the description, which are useful in the prophylaxis and in the treatment of diseases mediated by opioid receptors such as pruritus.

Not withstanding these and other disclosures of compounds useful as opioid receptor antagonists, there remains an unmet medical need for safe, effective and/or alternate treatment or prophylaxis of diseases associated with opioid receptors, particularly obesity and Related Diseases.

SUMMARY OF THE INVENTION

The present invention relates to a compound of the formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomers or mixtures thereof.

The present invention also provides a method of using a compound of formula I for the prevention, treatment and/or amelioration of the symptoms of obesity and Related Diseases.

The present invention also provides a pharmaceutical formulation comprising a compound of formula I in association with a carrier, diluent and/or excipient.

The present invention provides a compound of formula I having improved efficacy and bio-availability compared to compounds disclosed in U.S Patent 4,891,379 and European Patent application EP 1,072,592 A2.

The present invention relates to the use of a compound of formula I for the treatment and/or prophylaxis of obesity and Related Diseases including eating disorders (bulima, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression, anxiety, epileptic seizure, hypertension, cerebral hemorrhage, conjestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinenamia, substance abuse, drug overdose, compulsive behavior disorders (such as paw licking in dog), addictive behaviors such as gambling.

The present invention provides a compound of formula (I) useful for the manufacture of a medicament for the treatment, prevention and/or amelioration of symptoms associated with obesity, Related Diseases.

The present invention provides a compound of formula I useful in the treatment of obesity and related diseases with reduced potential for inhibition of cytochrome P450 enzyme.

In another embodiment, the present invention provides a compound of formula I or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomers or mixtures thereof, useful as an appetite suppressant.

DETAILED DESCRIPTION OF THE INVENTION

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

The term "mutual solvent" means a solvent that is used to dissolve two or more components of a reaction or mixture separately prior to reaction or mixing, that is a solvent common to more than one reagents or components of a mixture.

As used herein, the term "patient" includes human and non-human animals such as companion animals (dogs and cats and the like) and livestock animals. Livestock animals are animals raised for food production. Ruminants or "cud-chewing" animals such as cows, bulls, heifers, steers, sheep, buffalo, bison, goats and antelopes are examples of livestock. Other examples of livestock include pigs and avians (poultry) such as chickens, ducks, turkeys and geese. Also included are exotic animals used in food production such as alligators, water buffalo and ratites (e.g., emu, rheas or ostriches).

The preferred patient of treatment or prevention is a human.

The terms "treating" and "treat", as used herein, include their generally accepted meanings, *i.e.*, preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein.

The terms "preventing", "prevention of", "prophylaxis", "prophylactic" and "prevent" are used herein interchangeably and refer to reducing the likelihood that the recipient of a compound of formula I will incur or develop any of the pathological conditions, or sequela thereof, described herein.

As used herein, the term "effective amount" means an amount of a compound of formula I that is sufficient for treating a condition, or detrimental effects thereof, herein described, or an amount of a compound of formula I that is sufficient for antagonizing the opioid receptors to achieve the objectives of the invention.

The term "pharmaceutically acceptable" is used herein as an adjective and means substantially non-deleterious to the recipient patient.

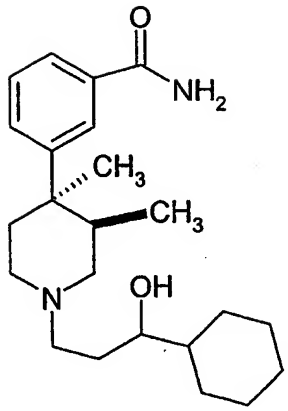
The term "formulation", as in pharmaceutical formulation, or "pharmaceutical composition" is intended to encompass a product comprising the active ingredient (compound of formula I), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the

ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutical carrier, or a compound of the formula I and a pharmaceutically acceptable co-antagonist of opioid receptors useful for the treatment and/or prevention of obesity or Related Diseases where antagonism of opioid receptors may be beneficial.

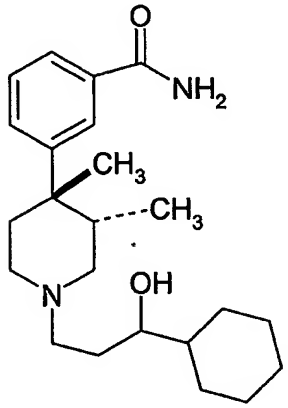
The terms "obesity and Related Diseases" or "Related Diseases" as used herein refers to such symptoms, diseases or conditions caused by, exacerbated by, induced by or adjunct to the condition of being obese. Such diseases, conditions and/or symptoms include but are not limited to eating disorders (bulima, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression, anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinenamia.

The term "cytochrome P450 enzyme" as used herein refers to the family of enzymes comprised of the cytochrome P450 system often called cyotchrome P's. It has become increasingly clear that inhibition of an enzyme or enzymes from this family is associated with deleterious effects which could be life threatening. For example, inhibition of the enzyme Cyp2D6, a member of the cytochrome P450 family, may cause serious drug-drug interactions and/or overdoses particularly in cases where patients are taking multiple medications. Thus, the present invention also relates to the use of a compound of formula I for the treatment or prevention of obesity and Related Diseases while minimizing undesirable drug-drug interactions in a patient who is also under medication with other drug(s) comprising administering a therapeutically effective amount of a compound of formula I to said patient.

The compound of the invention as illustrated in formula I occurs as the trans stereochemical isomer by virtue of the substituents at the 3- and 4-positions. More specifically, the group CH_3, at the 3-position is situated in a trans configuration relative to the CH_3 group at the 4-position. As such, the compound can exist as the trans (+) isomer of the formula



or the trans (-) isomer of the formula



The present invention comtemplates the individual trans (+) and (-) stereoisomers, as well as the mixture of the trans stereoisomers.

Also, for the group -CH_2CH_2C(OH)cyclohexyl there is the possibility of a chiral center, i.e. the carbon atom attached to the OH group is asymmetric. Therefore, the compound can further exist as the individual R or S stereoisomers, or the mixture of the isomers, and all are contemplated within the scope of the compounds of the present invention. A most preferred compound of the invention is trans(+)-1-[-3S-(3-hydroxy-3-cyclohexylpropyl)]-3(R),4(R)-dimethyl-4-(3-phenylcarboxamido) piperidine.

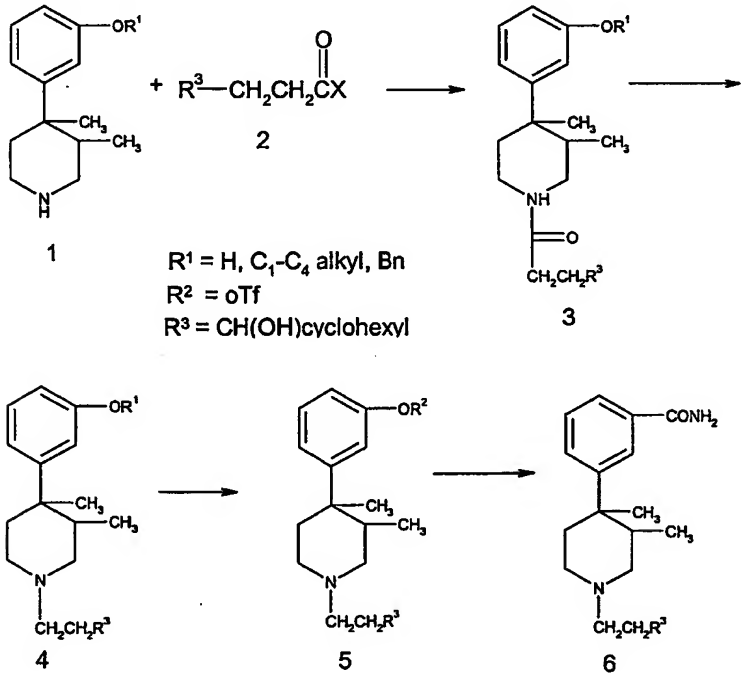
The compound of formula I forms pharmaceutically acceptable acid addition salts with a wide variety of inorganic and organic acids. The compound of formula I preferably exists as a pharmaceutically acceptable salt. More preferred is the hydrochloride, or the bisulfate salt of the compound of formula I.

In another embodiment, the compound(s) of the present invention has shown antiorexigenic effects, and is thus useful as an appetite suppressant. Reduction of food

intake over a period of time has been observed with rats fed a diet containing a compound of the invention. Interestingly the reduction in food intake was found to be more significant at each point in time for the compound of the present invention than with the clinical trial compound disclosed in U.S. Patent number 4,891,379.

Preparing the Compound of the Invention

The compound of the present invention may be prepared by a variety of procedures known to one of skill in the art. The preferred procedure involves transforming the OH group at the 3-position of the phenyl group of 3-,4-dimethyl-4-(3-hydroxyphenyl)piperidine into a good leaving group for example, by triflate formation or mesylate formation followed by a subsequent nucleophilic attack by a carbonyl group or synthon thereof. The carbonyl group or synthon thereof is then converted to the amide compound of formula I. The starting material 3,4-dimethyl-4-(3-substituted phenyl)piperidine (1) is reacted with an appropriate acylating agent (2) to provide the corresponding intermediate (3) which is reduced to the intermediate (4) and then converted to the compound of the present invention (6) via a triflate intermediate (5) under standard conditions as shown in Scheme 1.



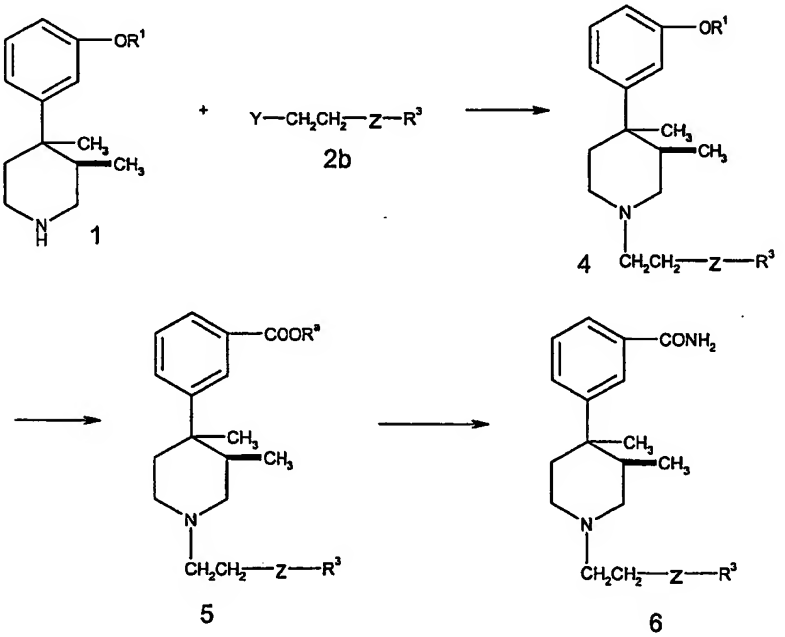
The first step of the above-described process wherein X is hydroxy, necessitates the use of coupling reagents commonly employed in the synthesis of peptides. Examples of such coupling reagents include the carbodiimides such as N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide, or N,N'-diethylcarbodiimide; the imidazoles such as carbonyldiimidazole; as well as reagents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ). The direct coupling of a substituted carboxylic acid and a 3-substituted-4-methyl-4-(3-substitutedphenyl)piperidine (1) is carried out by adding about an equimolar quantity of the piperidine starting material to a solution of the carboxylic acid in the presence of an equimolar quantity or slight excess of coupling reagent. The reaction generally is carried out in an unreactive organic solvent such as dichloromethane or N,N-dimethylformamide, and usually is complete within about twenty-four hours when conducted at a temperature of about 0 °C to about 30 °C. The product is then typically isolated by filtration. The acylated product (3) thus formed may be further purified, if needed, by any of several routine methods, including crystallization from common solvents, chromatography over solid supports such as silica or alumina, and related purification techniques.

The reaction (as in Scheme 1) wherein X is other than hydroxy is conducted as follows. The preferred leaving group in this reaction is where X is halogen, especially chloro. The reaction can be carried out by combining the substituted carboxylic acid derivative with about an equimolar quantity of the 3-substituted-4-methyl-4-(3-substituted phenyl)piperidine in a solvent such tetrahydrofuran, diethyl ether, dichloromethane, dioxane, dimethylsulfoxide, N,N-dimethylformamide, benzene, toluene, and the like. If desired, a base can be utilized in the acylation reaction when X is halogen to act as an acid scavenger. Commonly used bases include sodium carbonate, potassium carbonate, pyridine, triethylamine and related bases. Bases such as pyridine act as their own solvent and need no additional solvent. The reaction generally is substantially complete after about two to about 200 hours when carried out at a temperature of about 20 °C. to about 200 °C, preferably from about 30 °C to about 100 °C The product of the reaction may be isolated by simply removing the reaction solvent, for instance by evaporation under reduced pressure. Also, the reaction mixture may be added to water, and the product collected by filtration or extracted into a water immiscible solvent. The compound (3)

thus isolated can be further purified, if desired, by any of several well-known techniques. A suitable R^1 group for the above reaction is methyl, ethyl or the like.

The acylated intermediate (3) prepared as above is reduced according to standard procedures to provide the intermediate (4) useful in preparing the present compounds. Typical reducing agents suitable for use include the hydride reducing agents such as lithium aluminum hydride and sodium bis(2-methoxyethoxy)aluminum hydride, which is preferred. Typically, an excess of reducing agent is combined with the acylated intermediate in a mutual solvent. The reaction is substantially complete after about one to about 12 hours when conducted at a temperature in the range of about 20 °C to about 100 °C. The desired intermediate (4) may then be isolated by procedures well known to those of ordinary skill in the art.

The intermediate (4) may also be prepared by the direct substitution of a halogen substituted compound with the 3,4-dimethyl-4-(3-substituted phenyl)piperidine intermediate. This reaction is represented by the following scheme (2) wherein R^1 is hydrogen, C_1-C_4 alkyl, or benzyl; R^3 is cyclohexyl; Z is -CH(OH)-; and Y is halogen.



The above reaction (scheme 2) is conducted by combining approximately equimolar amounts of the two starting materials (compounds 1 and 2b) (salts, stereoisomers, and racemates thereof) in a mutual solvent. A slight excess of the halogen-substituted

compound (2b) may be employed to ensure complete reaction. Typical mutual solvents suitable for use in this reaction include aprotic solvents such as N,N-dimethylformamide and the like. Further, the reaction is preferably conducted in the presence of a base, such as sodium bicarbonate, which acts as an acid scavenger for the hydrohalic acid, which is formed as a by-product of the reaction. The reaction is generally complete after about 30 minutes to 24 hours when conducted at a temperature in the range of about 40 °C to about 100 °C. The product is isolated and purified, if needed, by standard procedures or isolation procedures described herein.

Other methods of preparing the intermediates (3) and/or (4) or analogs thereof, are disclosed in U.S Patent Nos. 4,081,450, and 4,191,771, European Patent application EP.1 072 592 A2 and references disclosed therein.

The intermediate (4) however prepared, is activated at the hydroxy group by reaction with a methane sulfonic anhydride, triflic anhydride, or other reagents known to one of skill in the art to convert the hydroxyl group to a good leaving group forming an isolatable intermediate triflate or mesylate. The intermediate triflate for example, is converted to the compound (5) by nucleophilic attack of a carbonyl group or synthon thereof followed by esterification. In a preferred mode of reaction, the carbonyl group is inserted by use of palladium reagents (carbonyl insertion reaction) often accompanied by *in-situ* esterification to afford the ester (5)(wherein R^a is C_1-C_4 alkyl or benzyl). The ester (5) is converted to the amide (6) by sealed tube ammonolysis conditions or other reaction conditions known to one of skill in the art. An alternate route involving direct conversion of a triflate intermediate to a carboxamide is illustrated in Wentland, et al., Biorganic and Medicinal Chemistry Letters 11 (2001) 623-626 and also in Wentland, et al., Biorganic and Medicinal Chemistry Letters 11 (2001) 1717-1721. For the compound of the present invention, the route involving converting the triflate to an isolable ester intermediate was found to be most workable and therefore preferred. Additional information for preparing the compound of formula I is available in the experimental section.

Salts of piperidines are prepared by methods commonly employed for the preparation of amine salts. In particular, acid addition salts of the piperidines are prepared by reaction of the piperidine with an appropriate acid of pKa less than about 4, generally in an unreactive organic solvent. Suitable acids include mineral acids such as hydrochloric, hydrobromic, hydriodic, sulfuric, phosphoric, and like acids. Organic acids

are also used, for example acetic acid, p-toluenesulfonic acid, chloroacetic acid, and the like. The usual solvents used in the reaction include acetone, tetrahydrofuran, diethyl ether, ethyl acetate, and the like. Quaternary salts can be prepared in generally the same way by reaction of the piperidne with an alkylsulfate or alkyl halide, for example, methyl sulfate, methyl iodide, ethyl bromide, propyl iodide, and the like.

The 3,4-dimethyl-4-(3-hydroxy- or -alkanoyloxyphenyl)piperidine derivative (1) employed as starting material in the synthesis of the compound of the present invention is prepared by the general procedures taught by Zimmerman in U.S. Pat. Nos.4,081,450, and 4,191,771 and references therein, and procedures disclosed in European Patent Application No. 1 072 592 A2 and known and applicable modifications thereof. The above references for the preparation of the starting material 3,4-dimethyl-4-(3-hydroxy- or -alkanoyloxyphenyl)piperidine derivative (1), are incorporated by reference in their entirety where applicable.

As noted above, the compounds of the present invention may exist as the resolved stereoisomers. The preferred procedure employed to prepare the resolved starting materials used in the synthesis of these compounds includes treating a 1,3-dialkyl-4-methyl-4-(3-alkoxyphenyl)piperidine with either (+)- or (-)-dibenzoyl tartaric acid to provide the resolved intermediate. This compound is dealkylated at the 1-position with vinyl chloroformate and finally converted to the desired 4-(3-hydroxyphenyl)piperidine isomer.

As will be understood by one skilled in the art, the individual trans stereoisomers of the compound of the present invention may also be isolated with either (+)- or (-)-dibenzoyl tartaric, or other resolving agents and/or techniques known to one of skill in the art, from the corresponding racemic mixture of the compound of the invention.

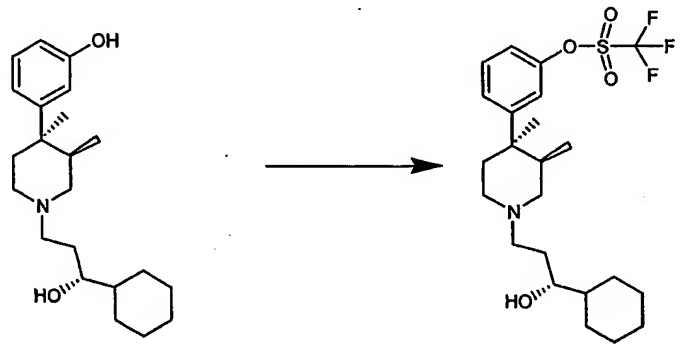
EXPERIMENTAL

The following Example illustrates a method for the preparation of the compound of the present invention.

Example

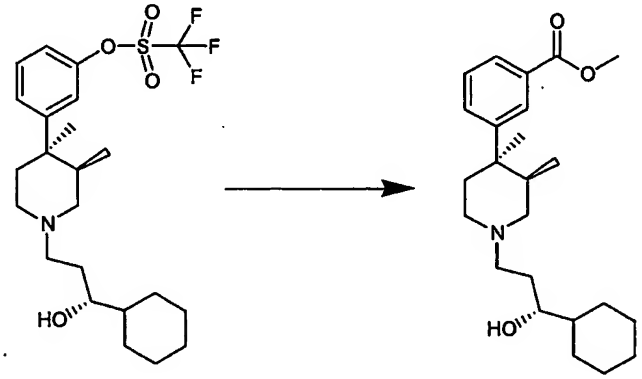
Synthesis of 3-[1-(3-Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide

Synthesis of Trifluoro-methanesulfonic acid 3-[1-(3-cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-phenyl ester



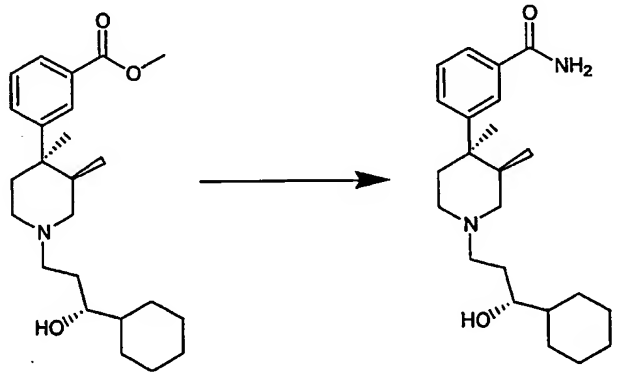
A 250mL round bottom flask equipped with an addition funnel and nitrogen inlet was charged with 2g (5.8mmol) of trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine prepared following the procedure disclosed in U.S. Patent number 4,191,771. The flask was then charged with 3.2mL (23.0mmol) of triethylamine, and 35mL of dichloromethane. While stirring at room temperature, 2.3g (6.4mmol) of N-phenyltrifluoromethanesulfonimide in 5mL of dichloromethane was added to the reaction dropwise via an addition funnel. The reaction mixture was stirred at room temperature for four hours. The reaction mixture was concentrated on a rotary evaporator to yield 4.3g of crude product. The crude product was purified by flash chromatography on silica gel eluting with 1% conc. ammonium hydroxide / 10% ethanol in chloroform to yield 2.0g (4.2mmol) of trifluoro-methanesulfonic acid 3-[1-(3-cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-phenyl ester. Electrospray MS M+1 ion = 478.6, H^1 NMR.

Synthesis of 3-[1-(3-Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzoic acid methyl ester



A 100mL sealed tube was charged with 2g (4.2 mmol) of trifluoro-methanesulfonic acid 3-[1-(3-cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-phenyl ester, 94mg (0.42mmol) of palladium acetate, 465mg (0.84mmol) of dppf, 1.29mL (9.2mmol) of triethylamine, 20mL of methanol, and 32mL of dimethylsulfoxide (DMSO). Carbon monoxide was bubbled subsurface into the reaction for about ten minutes. The tube was sealed and heated at 65°C for four hours. The reaction mixture was concentrated on a rotary evaporator to a residue. Water (approximately 100mL) was added to the residue followed by extraction of the organic phase with ethyl acetate (3x100mL). The organic extracts were dried over sodium chloride/sodium sulfate, filtered, and then concentrated to yield 2.4g of crude product. The crude product was purified by flash chromatography on silica gel eluting with 1% conc. ammonium hydroxide / 10% ethanol in chloroform to yield 0.7g (1.8mmol) of 3-[1-(3-cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzoic acid methyl ester. HPLC-MS = 100% M+1 ion 388.23.

Synthesis of 3-[1-(3-Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide



A reaction tube was charged with 0.7g (1.8mmol) of 3-[1-(3-cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzoic acid methyl ester, 5mg of sodium cyanide, and 30mL of methanol. Ammonia was bubbled subsurface into the reaction for ten minutes then the tube was sealed at heated at 85°C for sixteen hours. The reaction was driven to completion or substantial completion by daily addition of sodium cyanide and ammonia over a period of seven days or until the reaction was satisfactorily complete by HPLC analysis. Care is taken to cool the tube to between 0 ^{o}C and room temperature before addition of each new batch of sodium cyanide and ammonia. The reaction mixture

is concentrated on a rotary evaporator to yield 0.6g of crude product. The crude product is purified by flash column chromatography on silica gel eluting with 1% conc. ammonium hydroxide / 10% ethanol in chloroform to yield 260mg (0.7mmol) of 3-[1-(3-Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide. HPLC = 98%, Electrospray MS M+1 ion = 373.1, H^1 NMR.

Method of Using the Invention

As noted above, the compound of the present invention is useful in blocking the effect of agonists at mu, kappa, and/or delta receptors. As such, the present invention also provides a method for blocking a mu, kappa, delta or receptor combination (heterodimer) thereof in mammals comprising administering to a mammal requiring blocking of a mu, kappa, delta or combinations of mu, kappa, and/or delta receptors, a receptor blocking dose of a compound of formula I.

The term "receptor blocking dose", as used herein, means an amount of compound necessary to block a mu, kappa, or delta or receptor combination (heterodimer) thereof receptor following administration to a mammal requiring blocking of a mu, kappa, or delta or receptor combination (heterodimer) thereof receptor. The active compounds are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.05 to about 250 mg/kg of body weight. In the treatment of adult humans, the range of about 0.5 to about 100 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician in light of the relevant circumstances, including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. The compounds may be administered by a variety of routes such as the oral, transdermal, subcutaneous, intranasal, intramuscular and intravenous routes.

A variety of physiologic functions have been shown to be subject to influence by mu, kappa, or delta or receptor combination (heterodimers) thereof in the brain. As such, the compound of the present invention is believed to have the ability to treat a variety of disorders in mammals associated with these receptors such as eating disorders, opioid

overdose, depression, smoking, alcoholism, sexual dysfunction, shock, stroke, spinal damage and head trauma. As such, the present invention also provides methods of treating the above disorders at rates set forth above for blocking the effect of agonists at a mu, kappa, delta or receptor combination (heterodimer) thereof. The compound of the present invention has been found to display excellent activity in an opioid receptor binding assay which measures the ability of the compounds to block the mu, kappa, delta or receptor combination (heterodimer) thereof.

Futhermore, the compound of the present invention has been found to exhibit an unexpected and significant increase in efficacy compared to compounds disclosed in published European Patent application number 1 072592A2 (i.e. compound of example 2). The compound of the present invention is also unique because in addition to increased or comparable efficacy over disclosed compounds, it also provides significantly improved bioavailability characteristics. The increased efficacy and the superior bioavailability characteristics of the present compound were neither appreciated nor suggested by the prior art. Thus the compound of the present invention is believed to provide truly superior and unexpected advantages over the prior art (see Table (1) *infra*).

The assay for biological activity i.e. binding affinity was conducted using the following procedure.

GTPγS Binding Assay

An SPA - based GTPgS assay format was developed based on previous opioid (Emmerson et al., J. Pharm Exp Ther 278,1121,1996; Horng et al., Society for Neuroscience Abstracts, 434.6, 2000) and muscarinic (DeLapp et al., JPET 289, 946, 1999) assay formats. Membranes were resuspended in 20 mM HEPES, 100 mM NaCl, 5 mM MgCl2, 1 mM DTT, and 1 mM EDTA. Fifty mL of GTPγ[35S], compound, membrane suspension (20 microgram/well), and wheat germ agglutinin coated SPA beads (1mg/well) were added to clear bottom 96 well assay plates. GDP (200 mM) was added to the membrane solution prior to addition to the assay plates. Plates were sealed and incubated for four hours at room temperature then placed in a refrigerator overnight to allow the beads to settle. Signal stability at 4 °C was determined to be > 60 hours. Plates were warmed to room temperature and counted in a Wallac Microbeta scintillation counter. For antagonist assays, specific agonists were added at the following concentrations: (MOR) DAMGO 1 micromolar, (DOR) DPDPE 30 nM, (KOR) U69593

300 nM. Kb's were determined by Cheng-Prusoff equation (Cheng and Prusoff, 22,3099 1973).

Table 1 provides a summary of in vitro activity in a GTP-γ-S functional antagonist assay. This data shows that the compound of formula I is at least 2 fold more potent than the compound of formula (II) (the closest compound exemplified in European Patent application No. 1072592 A2), and comparable potency compared to compound (III), a previous clinical trial candidate discontinued for unacceptable bioavailability which is disclosed and claimed in U.S. Patent No. 4,891,379.

Table 1

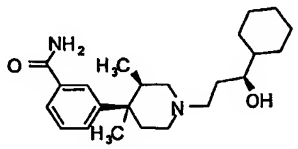
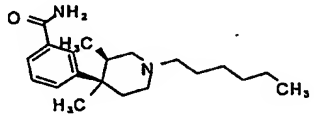
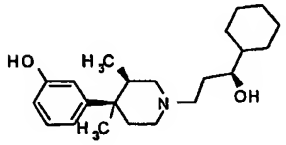
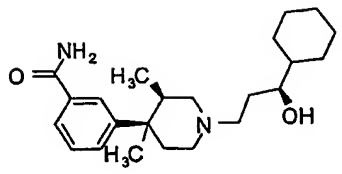
Compound		In Vitro GTPγ-S human opioid receptors expressed in Mu nM	Kappa nM	Delta nM
(I)		0.12	1.93	2.81
(II)		0.31	4.51	8.72
(III)		0.04	0.32	1.19

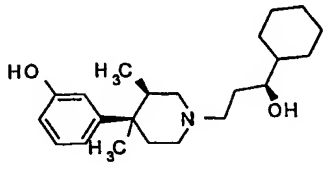
Table 2 provides data showing that the compound of formula (I) also shows better bioavailability than the compound of formula (III), a previous clinical trial candidate disclosed and claimed in U.S. Patent No. 4,891,379.

Table 2

Metabolis
Rat

(I) 

32

(II) 

2.5

The compound of formula I, in addition to increased efficacy and bio-availability compared to previously disclosed compounds, also exhibits a significantly reduced potential for inhibiting the cytochrome P450 enzyme system, a surprising and unexpected finding that spells improved safety and reduced potential for drug-drug interactions etc. The reduced potential for inhibition of cytochrome P450 was discovered using a standard assay that monitors the compound's ability to inhibit Cyp2D6 a member of the cytochrome P450 family of enzymes. The protocol and comparative results are provided below.

Assay for Inhibition of CYP2D6 activity

The inhibition of human Cytochrome 2D6 (CYP2D6) activity was studied using a validated high through-put screening assay. A 3 uL aliquot of an 8 mM stock solution of compound was delivered to 397 uL of pH 7.4 (50mM) phosphate buffer resulting in an initial concentration of 60uM. The compound dose solutions were prepared by serial dilutions to produce concentrations of 60, 19.4, 6.28, 2.03,0.66, 0.21, 0.069, and 1 uM. A 6 mM NaDPH stock solution was prepared by addition of 100mg of NaDPH to 20 mL of pH 7.4 buffer. A 600uL aliquot of Human liver Microsomes (HLM - 20.0 mg/ml) was added to 20 ml of pH 7.4 phosphate buffer to produce a 0.6 mg/ml solution of HLM. To the HLM mixture was added 120 uL of a 10 mM bufurolol solution (CYP2D6 substrate) producing a final bufuralol concentration of 60 uM. To each assay plate was added 100 uL of the compound dose solutions, 25 uL NaDPH and 25 uL HLM/bufurolol solution.

Samples were incubated at 37 °C for 10 minutes and the reaction was quenched with 25 uL of a 2% perchloric acid solution, followed by centrifugation at 3200 rpm for 30 min. The resulting supernatant was assayed for bufurolol concentrations using a Turbo Ion Spray API 150EX MS method. The calculated IC50 value represents the compound concentration that results in a 50% reduction in burfurolol consumption. Table 3 below provides a comparative data for inhibition of CyP2D6

Table 3

Compound #	Cyp2D6 IC_{50}
I	38.96
II	2.46
III	9.27

Table 3 shows that the compound of formula I is nearly 16 times less likely to cause inhibition of the cytochrome P450 enzyme compared to the prior clinical trial candidate compound (II) claimed in U.S. Patent No. 4,891,379. Furthermore, the data shows that the compound of formula (I) is over 4 times less likely to inhibit the cytochrome P450 enzyme system compared to the compound of formula (III) which is disclosed as example 2 in European Patent application number 1072592 A2 published January 31, 2001.

Antiorexigenic effect

Compounds were tested for effects on food consumption in male Long-Evans rats which had been fasted for 18 hours prior to testing. The weight of food consumed was measured for groups of 6 rats treated with test substance and compared to the food consumed by an untreated control group of 6 animals. Oral administration of a 3 mg/kg dose of a compound of formula I resulted in a statistically significant inhibition of cumulative food consumed, as measured over 1hour, 2 hour and 4 hour time periods. Oral administration of a 3 mg/kg dose of the previous clinical trial compound (II) disclosed in U.S Patent No. 4,891,379 did not produce statistically significant inhibition of food consumption over the same time periods.

Formulation

While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of the invention. Such compositions will contain from about 0.1 percent by weight to about 90.0 percent by weight of a present compound. As such, the present invention also provides pharmaceutical formulations comprising a compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient therefor.

In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material that acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium, and soft and hard gelatin capsules.

Examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a

predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

In order to more fully illustrate the operation of this invention, the following formulation examples are provided. The examples are illustrative only, and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the compounds of the present invention.

FORMULATION 1

Hard gelatin capsules are prepared using the following ingredients:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	250	55
Starch dried	200	43
Magnesium stearate	10	2

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

FORMULATION 2

Capsules each containing 20 mg of medicament are made as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	20	10
Starch	89	44.5
Microcrystalline cellulose	89	44.5
Magnesium stearate	2	1

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

FORMULATION 3

Capsules each containing 100 mg of active ingredient are made as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	100	30
Polyoxyethylene Sorbitan monooleate	50mcg	0.02
Starch powder	250	69.98

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

FORMULATION 4

Tablets each containing 10 mg of active ingredient are prepared as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	10	10
Starch	45	45
Microcrystalline cellulose	35	35
Polyvinylpyrrolidone (as 10% solution in water)	4	4
Sodium carboxymethyl starch	4.5	4.5
Magnesium stearate	0.5	0.5

talc	1	1

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50-60 °C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

FORMULATION 5

A tablet formula may be prepared using the ingredients below:

Compound	Amount per capsule (mg)	Percent by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	250	38
Cellulose microcrystalline	400	60
Silicon dioxide fumed	10	1.5
Stearic acid	5	0.5

The components are blended and compressed to form tablets each weighing 665 mg.

FORMULATION 6

Suspensions each containing 5 mg of medicament per 5 ml dose are made as follows:

Compound	Amount per 5mL suspension (ml)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	5
Sodium carboxymethyl cellulose	50
Syrup	1.25

Benzoic acid solution	0.10
Flavor	q.v.
Color	q.v.
Water	q.s. to 5mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the paste with stirring. Sufficient water is then added to produce the required volume.

FORMULATION 7

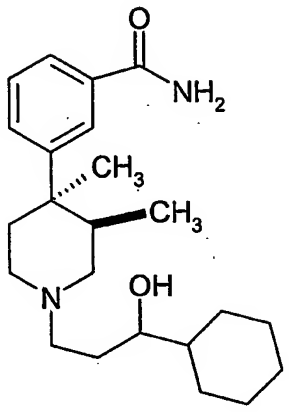
An aerosol solution is prepared containing the following components:

Compound	Concentration by weight (percent)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide hydrochloride	0.25
Ethanol	29.75
Propellant 22 (chlorodifluoromethane)	70.0

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.

We claim:

1. A compound of the formula I:



(I)

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomers or mixtures thereof.

2. The compound of claim 1 which is the (+)-trans isomer.

3. The compound of claim 1 which is trans(+)-1-[-3S-(3-hydroxy-3-cyclohexylpropyl)]-3(R),4(R)-dimethyl-4-(3-phenylcarboxamido)piperidine.

4. A pharmaceutical composition having as an active ingredient an effective amount of a compound of formula I.

5. A pharmaceutical composition containing the compound of formula I in association with a carrier and/or diluent.

6. A method for blocking a mu, kappa, delta or receptor combination (heterodimer) thereof in mammals comprising administering to a mammal requiring blocking of a mu, kappa, delta or receptor combination (heterodimer) thereof, a receptor

blocking dose of a trans-3,4 isomer of a compound of the formula I, or a pharmaceutically acceptable salt, enantiomer, racemate, mixture of diastereomers, or solvate thereof.

7. A method of treating or preventing obesity and Related Diseases comprising administering a therapeutically effective amount of a compound of formula I to a patient in need thereof.

8. A method according to Claim 6 wherein the Related Diseases is selected from the group consisting of diabetes, diabetic complications, diabetic retinopathy, atherosclerosis, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinamia.

9. Use of a compound of formula I in the treatment of diseases related to obesity including irritable bowel syndrome, nausea, vomiting, depression, smoking and alcohol addiction, sexual dysfunction, substance abuse, drug overdose, addictive behavior disorders, compulsive behaviors, and stroke.

10. Use of a compound of formula I in the manufacture of a medicament for the treatment and/or amelioration of the symptoms associated with obesity and Related Diseases comprising administering a therapeutically effective amount of a compound of formula I to a patient in need thereof.

11. Use of a compound of formula I for the treatment or prevention of obesity and Related Diseases while minimizing undesirable drug-drug interactions in a patient who is also under medication with other drug(s) comprising administering a therapeutically effective amount of a compound of formula I to said patient.

12. Use of a compound of formula I as an appetite suppressant comprising administering a therapeutically effective amount of a compound of formula I to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

PCT/US 03/14540

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/14 A61K31/445 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	C. H. MITCH: "3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines: opioid antagonists with potent anorectant activity" J. MED. CHEM., vol. 36, no. 20, 1993, pages 2842-50, XP002249614 example 11	1-12
A	US 4 891 379 A (ZIMMERMAN DENNIS M ET AL) 2 January 1990 (1990-01-02) cited in the application example 23	1-12
A	EP 1 072 592 A (PFIZER LTD ;PFIZER (US)) 31 January 2001 (2001-01-31) cited in the application example 2	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2003	13/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WENTLAND M P ET AL: "8-Carboxamidocyclazocine analogues - redefining the structure-activity relationships of 2,6-methano-3-benzazocines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 5, 12 March 2001 (2001-03-12), pages 623-626, XP004230076 ISSN: 0960-894X cited in the application page 623, column 2 -----	1-12

INTERNATIONAL SEARCH REPORT

PCT/US 03/14540

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-9,11-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US 03/14540

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		US 2002099216 A1	25-07-2002

US 20020099216A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2002/0099216 A1

Gibson et al. (43) Pub. Date: Jul. 25, 2002

(54) COMPOUNDS USEFUL IN THERAPY

(75) Inventors: **Stephen Paul Gibson**, Sandwich (GB); **Ivan Tommasini**, Sandwich (GB); **David Morris Gethin**, Sandwich (GB); **Richard Edward Armer**, Newhouse (GB)

Correspondence Address:
SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, NY 11530 (US)

(73) Assignee: **Pfizer Inc.**, New York, NY

(21) Appl. No.: **10/108,160**

(22) Filed: **Mar. 27, 2002**

Related U.S. Application Data

(63) Continuation of application No. 09/575,951, filed on May 23, 2000, now abandoned.

(30) **Foreign Application Priority Data**

May 28, 1999 (GB) GB9912411.7

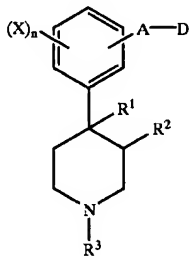
Publication Classification

(51) **Int. Cl.**[7] **C07D 417/02**; C07D 413/02; C07D 43/02; C07D 41/02; C07D 211/32; C07D 211/26

(52) **U.S. Cl.** **546/208**; 540/597; 544/60; 544/129; 544/360; 546/229; 546/235

(57) **ABSTRACT**

There is provided a compound of formula I,



I

wherein A, D, R^1, R^2, R^3, X and n have meanings given in the description, which are useful in the prophylaxis and in the treatment of diseases mediated by opiate receptors, such as pruritus.

COMPOUNDS USEFUL IN THERAPY

[0001] This invention relates to pharmaceutically useful compounds, in particular compounds that bind to opiate receptors (e.g. mu, kappa and delta opioid receptors).

[0002] Compounds that bind to such receptors are likely to be useful in the treatment of diseases mediated by opiate receptors, for example irritable bowel syndrome; constipation; nausea; vomiting; and pruritic dermatoses, such as allergic dermatitis and atopy in animals and humans. Compounds that bind to opiate receptors have also been indicated in the treatment of eating disorders, opiate overdoses, depression, smoking and alcohol addiction, sexual dysfunction, shock, stroke, spinal damage and head trauma.

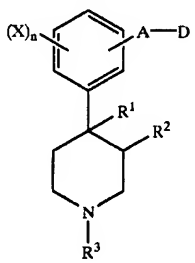
[0003] There is a particular need for an improved treatment of itching. Itching, or pruritus, is a common dermatological symptom that can give rise to considerable distress in both humans and animals. Pruritus is often associated with inflammatory skin diseases which may be caused by hypersensitivity reactions, including reactions to insect bites, such as flea bites, and to environmental allergens, such as house dust mite or pollen; by bacterial and fungal infections of the skin; or by ectoparasite infections.

[0004] Existing treatments that have been employed in the treatment of pruritus include the use of corticosteroids and antihistamines. However, both of these treatments are known to have undesirable side effects. Other therapies that have been employed include the use of essential fatty acid dietary supplements, though these have the disadvantages of being slow to act, and of offering only limited efficacy against allergic dermatitis. A variety of emollients such as soft paraffin, glycerine and lanolin are also employed, but with limited success.

[0005] Thus, there is a continuing need for alternative and/or improved treatments of pruritus.

[0006] Certain 4-arylpiperidine-based compounds are disclosed in inter alia European patent applications EP 287339, EP 506468, EP 506478 and *J. Med. Chem.* 1993, 36, 2833-2850 as opioid antagonists. In addition, International Patent Application WO 95/15327 discloses azabicycloalkane derivatives useful as neuroleptic agents.

[0007] According to the invention there is provided compounds of formula I:



I

[0008] wherein

[0009] A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH;

[0010] D represents H, OH, CN, $N(R^4)(R^5)$, $N(H)R^6$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$;

[0011] provided that when A represents C_{2-4} alkenylene or C_{2-4} alkynylene, and D represents OH, $N(R^4)(R^5)$ or $N(H)R^6$, then D is not directly attached to an unsaturated carbon atom;

[0012] and provided that when A represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$;

[0013] R^4 and R^5 independently represent H, C_{1-4} alkyl, C_{3-8} cycloalkyl, aryl,

[0014] C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^4 and R^5, together with the N-atom to which they are attached, form a 4- to 7-membered heterocyclic ring, which ring optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur and which ring is optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, =O, nitro, amino or halo;

[0015] R^6 represents $C(O)R^{10a}$, $C(O)OR^{10b}$ or $S(O)_2R^{10c}$;

[0016] R^{10a} to R^{10c} independently represent C_{1-4} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl (which four groups are all optionally substituted by or one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), or R^{10a} represents H;

[0017] R^7 and R^8 independently represent H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

[0018] R^{9a} and R^{9b} independently represent C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^{9b} represents H;

[0019] R^1 and R^2 are each independently H or C_{1-4} alkyl;

[0020] R^3 represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and $-N(R^{11a})(R^{11b})$), C_{1-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one

or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{12a})S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $—W—A^1—N(R^{12b})(R^{12c})$;

[0021] p is 0, 1 or 2;

[0022] W represents a single bond, C(O) or $S(O)_q$;

[0023] A^1 represents a single bond or C_{1-10} alkylene; provided that when both W and A^1 represent single bonds, then the group $—N(R^{12b})(R^{12c})$ is not directly attached to an unsaturated carbon atom;

[0024] q is 0, 1 or 2;

[0025] R^{11a} to R^{11d} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)) or Het^2;

[0026] provided that R^{11d} does not represent H when p represents 1 or 2;

[0027] R^{12a} to R^{12c} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het^3, or R^{12b} and R^{12c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally interrupted by O, S and/or an $N(R^{14})$ group and is optionally substituted by one or more C_{1-4} alkyl groups;

[0028] R^{13} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, nitro, amino or halo;

[0029] R^{14} represents H, Can alkyl, C_{3-8} cycloalkyl, A_2-(C_{3-8} cycloalkyl) or A^2-aryl;

[0030] A^2 represents C_{1-6} alkylene;

[0031] Het^1, Het^2 and Het^3 independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);

[0032] X is H, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

[0033] n is 0, 1 or 2;

[0034] or pharmaceutically, or veterinarily, acceptable derivatives thereof;

[0035] which compounds are referred to together hereinafter as "the compounds of the invention."

[0036] In the definitions used herein, alkyl, alkylene, alkoxy, alkoxy carbonyl, alkanoyl, alkanoyloxy, alkenyl, alkynyl and the alkyl parts of alkylphenyl and aryl alkoxy groups may, when there is a sufficient number of carbon atoms, be straight or branched-chain and/or optionally interrupted by one or more oxygen and/or sulfur atom(s). The term halo includes fluoro, chloro, bromo or iodo. The term "aryl" includes optionally substituted phenyl, naphthyl and the like, and "aryloxy" includes optionally substituted phenoxy and naphthyloxy and the like. Unless otherwise specified, aryl and aryloxy groups are optionally substituted by one or more (e.g. one to three) substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkoxy carbonyl and C_{1-5} alkanoyl (which latter four groups are optionally substituted by one or more halo atoms).

[0037] The heterocyclic rings that Het^1, Het^2 and Het^3 represent and that $N(R^4)(R^5)$ may represent, may be fully saturated, partially unsaturated and/or wholly or partially aromatic in character.

[0038] For the avoidance of doubt, when heterocyclic groups (i.e. Het^1, Het^2, Het^3 and some definitions of $N(R^4)(R^5)$) are at least part-saturated, possible points of substitution include the atom (e.g. the carbon atom) at the point of attachment of the heterocyclic group to the rest of the Molecule. Het (Het^1, Het^2 and Het^3) groups may also be attached to the rest of the molecule via a heteroatom.

[0039] The piperidine moiety in compounds of formula I may be in N-oxidised form. Sulfur atoms that may interrupt (e.g. alkyl) substituents in compounds of formula I may be present in oxidised form (e.g. as sulfoxides or sulfones). All heterocyclic groups (i.e. Het^1, Het^2, Het^3 and some definitions of N(R)(R)) may also be in N- or S-oxidized forms.

[0040] The term "pharmaceutically, or veterinarily, acceptable derivatives" includes non-toxic salts. Salts which may be mentioned include: acid addition salts, for example, salts formed with sulfuric, hydrochloric, hydrobromic, phosphoric, hydroiodic, sulfamic, organo-sulfonic, citric, carboxylic (e.g. acetic, benzoic, etc.), maleic, malic, succinic, tartaric, cinnamic, ascorbic and related acids; base addition salts; salts formed with bases, for example, the sodium, potassium and C_{1-4} alkyl ammonium salts.

[0041] The compounds of the invention may also be in the form of quaternary ammonium salts, e.g. at the piperdine moiety, which salts may be formed by reaction with a variety of alkylating agents, such as an alkyl halide or an ester of sulfuric, or an aromatic sulfonic, acid.

[0042] The compounds of the invention may exhibit tautomerism. All tautomeric forms of the compounds of formula I are included within the scope of the invention.

[0043] The compounds of the invention contain one or more asymmetric centres and thus they can exist as enantiomers and diastereomers. Diastereoisomers may be separated using conventional techniques e.g. by fractional crystallisation or chromatography. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional techmiques e.g. fractional crystallisation or HPLC. The desired optical isomers may be prepared by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation. Alternatively, the desired optical isomers may be prepared by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid or base. The invention includes the use of both the separated individual isomers as well as mixtures of isomers.

[0044] Also included within the scope of the invention are radiolabelled derivatives of compounds of formula I which are suitable for biological studies.

[0045] Preferred compounds of the invention include those wherein:

[0046] The group A-D is attached in the meta-position relative to the piperidine ring;

[0047] R^1 represents C_{1-2} alkyl;

[0048] R^2 represents H or C_{1-2} alkyl;

[0049] R^3 represents saturated C_{1-10} (e.g. C_{1-8}) alkyl, optionally substituted by one or more substituents selected from OR^{11c}, CN, halo, C_{2-4}, alkanoyl, C_{1-4} alkoxy carbonyl, $N(R^{12a})SO_2R^{13}$, Het^1, aryl (which latter group is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$), or $—W—A^1—N(R^{12b})(R^{12c})$;

[0050] R^{11c} represents H, C_{1-6} alkyl or aryl (which latter groups is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$);

[0051] R^{12a} to R^{12c} independently represent H, C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which latter three groups are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy);

[0052] R^{13} represents C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which three groups are all optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy);

[0053] W represents C(O);

[0054] A^1 represents a single bond.

[0055] More preferred compounds of the invention include those wherein:

[0056] A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more OH and/or methyl groups;

[0057] D represents H, OH, CN, $N(H)R^4$, $N(H)C(O)R^{10a}$, $N(H)C(O)OR^{10b}$, $N(H)S(O)_2R^{10c}$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$ or $C(=NOH)R^8$;

[0058] R^4 and R^5 independently represent H, C_{1-4} alkyl or C_{1-3} alkylphenyl (which latter two groups are both optionally substituted by C_{1-4} alkoxy);

[0059] R^7 and R^8 independently represent H or C_{1-4}alkyl;

[0060] R^{10a} to R^{10c} independently represent C_{1-4} alkyl (optionally substituted by one or more halo atoms);

[0061] R^1 represents methyl;

[0062] R^2 represents H or methyl;

[0063] R^3 represents saturated C_{1-7} alkyl, optionally substituted by one or more substituents selected from CN, OR^{11c} or phenyl;

[0064] R^{11c} represents C, alkyl or phenyl;

[0065] X represents halo, particularly fluoro;

[0066] n represents 1 or, preferably, 0.

[0067] Particularly preferred compounds of the invention include those wherein:

[0068] A represents a single bond, $—CH_2—$, $—CH(CH_3)—$, $—C(CH_3)_2—$, $—CH(OH)—$, $—(CH_2)_2—$, $—CH=CH—$, or $—C≡C—$;

[0069] D represents H, OH, CN, NH_2, $N(H)CH_3$, CHO, CH(=NOH), $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, $C(O)N(H)CH_3$, C(O)N(H)Et, C(O)N(H)(2-MeOEt), C(O)N(H)n-Pr, C(O)N(H)i-Pr, C(O)N(H)n-Bu, C(O)N(H)i-Bu, C(O)N(H)t-Bu, $C(O)N(H)CH_2Ph$, $C(O)N(CH_3)_2$, $C(O)N(Et)_2$, $N(H)C(O)CH_3$, $N(H)C(O)OCH_3$, $N(M)S(O)_2CH_3$ or $N(H)S(O)_2CF_3$;

[0070] R^1 and R^2 represent methyl groups in the mutually trans configuration;

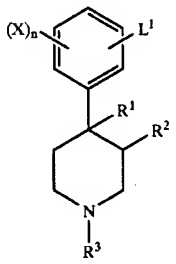
[0071] R^3 represents benzyl, 5-cyanopentyl, n-hexyl, 5-methylhexyl, 2-phenoxyethyl or 3-phenylpropyl.

[0072] Preferred compounds of the invention include the compounds of the Examples described hereinafter.

[0073] According to a further aspect of the invention there is provided processes for the preparation of compounds of the invention, as illustrated below.

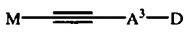
[0074] The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

[0075] 1. Compounds of formula I in which A represents C_{2-4} alkynylene (in which group the carbon-carbon triple bond is α,β to the benzene ring), which alkynylene group is optionally substituted at the 3- and/or the 4-C (relative to the benzene ring) by one or more substituents defined hereinbefore in respect of A, and/or one of the groups defined hereinbefore in respect of D, or (when D is not attached at the 3- or 4-C) which alkynylene group is substituted at the 2-C (relative to the benzene ring) by CN, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, may be prepared by reaction of a corresponding compound of formula II,



II

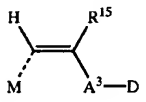
[0076] wherein L^1 is a suitable leaving group such as halogen, preferably bromine or iodine, or a sulfonate such as trifluoromethanesulfonate, and R^1, R^2, R^3, X and n are as hereinbefore defined, with a compound of formula III,



III

[0077] wherein M represents (as appropriate) H, a tin-containing moiety (e.g. tributylstannyl), a boron derivative (e.g. a boronic acid), a zinc halide, a magnesium halide or an alkali metal (which latter three groups may be formed in situ from the corresponding halide), A^3 represents a single bond or C_{1-2} alkylene (optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH or halo), and D is as hereinbefore defined, provided that when A^3 represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$, wherein R^4, R^5 and R^6 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable catalyst system (e.g. bis(triphenylphosphine)palladium(II) chloride combined with copper(I) iodide) and an appropriate organic base (e.g. triethylamine).

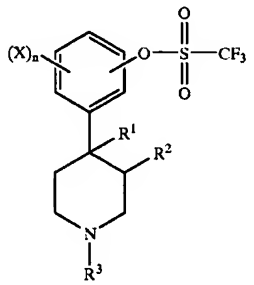
[0078] 2. Compounds of formula I in which A represents C_{2-4} alkenylene (in which group the carbon-carbon double bond is α,β to the benzene ring), which alkenylene group is optionally substituted at the 2-C (relative to the benzene ring) by C_{1-4} alkyl, and also optionally substituted at the 3- and/or 4-C (relative to the benzene ring) by one or more of the substituents defined hereinbefore in respect of A and/or one of the groups defined hereinbefore in respect of D, or which alkenylene group is substituted at the 2-C (relative to the benzene ring) by CN, $C(O)N(R^4)^5$), $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, may be prepared by reaction of a corresponding compound of formula II, as hereinbefore defined, with a compound of formula IV,



IV

[0079] wherein the dashed bond represent optional cis- or trans-geometry, R^{15} represents H or C_{1-4} alkyl, and A^3, D and M are as hereinbefore defined, for example at between room temperature and reflux temperature in the presence of a reaction-inert solvent (e.g. 1,4dioxan. or THF), an appropriate catalyst (e.g. tetrakis(triphenylphosphine-)palladium(0) or bis(triphenylphosphine)palladium(II) acetate) and either (as appropriate) a suitable source of halide ion (e.g. lithium chloride) or a suitable base (e.g. tricthylamine).

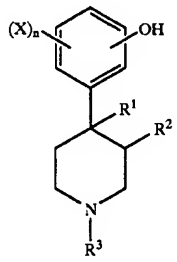
[0080] 3. Compounds of formula I in which A represents a single bond and D represents CN may be prepared by reaction of a compound of formula V,



V

[0081] wherein R^1, R^2, R^3, X and n are as hereinbefore defined with an alkali metal cyanide (e.g. potassium cyanide), for example at raised temperature in the presence of a reaction-inert solvent (e.g. N-methylpyrrolidine) and a suitable catalyst (e.g. palladium(II) acetate combined with 1,1'-bis(diphenylphosphino)ferrocene).

[0082] Compounds of formula V may be prepared by reaction of a corresponding compound of formula VI,

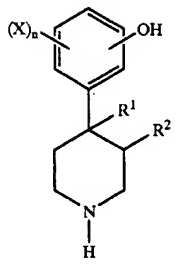


VI

[0083] wherein R^1, R^2, R^3, X and n are as hereinbefore defined, with an appropriate triflating agent (e.g. N-phenyl-trifluoromethanesulfonimide), for example at between 0° C. and room temperature in the presence of a reaction-inert organic solvent (e.g. dichloromethane) and a suitable base (e.g. triethylamine).

[0084] Compounds of formula VI may be prepared by reaction of a corresponding compound of formula VII,

VII



[0085] in which R^1, R^2, X and n are as hereinbefore defined, with a compound of formula VIII,

$R^3—L^1$ VIII

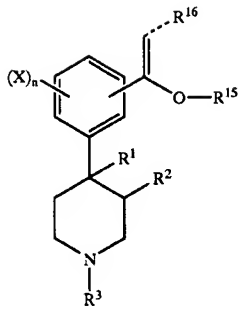
[0086] wherein R^3 and L^1 are as hereinbefore defined, under conditions that are known to those skilled in the art, which include, for example, alkylation at between room temperature and reflux temperature in the presence of a reaction-inert organic solvent (e.g. N,N-dimethylformamide) and a suitable base (e.g. $NaHCO_3$), and arylation at between room temperature and reflux temperature in the presence of a suitable catalyst system (e.g. tris(dibenzylideneacetone)palladium(0) combined with tri-o-tolylphosphine), an appropriate strong base (e.g. sodium tert-butoxide) and a reaction-inert solvent (e.g. toluene).

[0087] 4. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents NH_2 (which is attached to a CH_2 group) may be prepared by reduction of a; corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents CN, for example at between room and reflux temperature in the presence of a suitable reducing agent (e.g. lithium aluminium hydride) and an appropriate solvent (e.g. THF).

[0088] 5. Compounds of formula I in which D represents $C(O)NH_2$ may be prepared by controlled hydrolysis of a corresponding compound of formula I in which D represents CN, for example by reaction with polyphosphoric acid at between 50 and 150° C.

[0089] 6. Compounds of formula I in which A represents a single bond and D represents C(O)—(C_{1-6} alkyl) or C(O)—(C_{1-4} alkylphenyl), which alkyl and alkylphenyl groups are both optionally substituted by one or more of the substituents defined hereinbefore in respect of R^8, may be prepared by hydrolysis of a corresponding compound of formula IX,

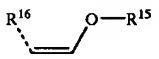
IX



[0090] wherein R^{15} represents C_{1-6} alkyl, R^{16} represents H, C_{1-5} alkyl, phenyl or C_{1-3} alkylphenyl which latter three groups are all optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), the dashed bond indicates optional cis- or trans-geometry, and R^1, R^2, R^3, X and n are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. by reaction at between room and reflux temperature with an aqueous solution of a mineral acid).

[0091] Compounds of formula IX may be prepared by reaction of a compound of formula II, as hereinbefore defined, with a compound of formula X,

X



[0092] wherein the dashed bond indicates optional cis- or trans-geometry, and R^{15} and R^{16} are as hereinbefore defined, for example at between room temperature and reflux temperature in the presence of an appropriate catalyst (e.g. palladium(II) acetate combined with 1,1'-bis(diphenylphosphino)ferrocene), an organic base (e.g. triethylamine) and an appropriate solvent (e.g. N,N-dimethylformamide).

[0093] 7. Compounds of formula I in which D represents $C(O)R^8$, wherein R^8 is as hereinbefore defined provided that it does not represent H, may be prepared by reaction of a corresponding compound of formula I in which D represents CN with an organometallic compound capable of delivering an R^{8a}-containing anion (e.g. an appropriate organolithium or Grignard reagent), wherein R^{8a} is defined as for R^8 above provided that it does not represent H, for example at between −80 and 10° C. in the presence of a reaction-inert organic solvent (e.g. tetrahydrofuran).

[0094] 8. Compounds of formula I in which A represents a single bond and D represents $C(O)OR^7$, wherein R^7 is as hereinbefore defined provided that it does not represent H, may be prepared by reaction of a corresponding compound of formula V, as hereinbefore defined, with carbon monoxide and an alcohol of formula $R^{7a}OH$, wherein R^{7a} is defined as for R^7 above provided that it does not represent H, for example in the presence of a suitable transition-metal cata-

lyst system (e.g. palladium(II) acetate combined with 1,1'-bis(diphenylphosphino)ferrocene) and a reaction-inert solvent (erg. DMF).

[0095] 9. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH (which is attached to a CH_2 group) may be prepared by reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as hereinbefore defined, for example at between 0° C. and reflux temperature in the presence of a suitable reducing agent (e.g. lithium aluminium hydride) and an appropriate solvent (e.g. THF).

[0096] 10. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are gem-disubstituted with two C_{1-4} alkyl groups (a to D) and are optionally substituted by one or more further substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH, may be prepared by reaction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as hereinbefore defined, with a suitable C_{1-4} alkyl-delivering organometallic compound (e.g. an alkylmagnesium halide), for example at between −10° C. and reflux temperature in the presence of a suitable solvent (e.g. THF).

[0097] 11. Compounds of formula I in which D represents $C(O)N(R^4)(R^5)$, wherein R^4 and R^5 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, and R^{7a} is as hereinbefore defined, with a compound of formula XI,

$$HN(R^4)(R^5) \qquad XI$$

[0098] or an acid (e.g. HCl) addition salt thereof, wherein R^4 and R^5 are as hereinbefore defined, for example at a temperature of between −10 and +150° C. and a pressure of between 1 and 10 atmospheres, optionally in the presence (as appropriate) of a Lewis-acidic catalyst (e.g. trimethylaluminium) and a reaction-inert solvent (e.g. toluene).

[0099] 12. Compounds of formula I in which D represents $C(O)N(R^4)(R^5)$, wherein R^4 and R^5 are as hereinbefore defined, may alternatively be prepared by reaction of a corresponding compound of formula I in which D represents C(O)OH with a compound of formula XI, as hereinbefore defined, under coupling conditions known to those skilled in the art.

[0100] 13. Compounds of formula I in which D represents C(O)OH may be prepared by hydrolysis of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, wherein R^{7a} is as hereinbefore defined, under conditions that are known to those skilled in the art.

[0101] 14. Compounds of formula I in which D represents $N(H)R^6$, wherein R^6 is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which D represents NH_2 with a compound of formula XII,

$$R^6—L^1 \qquad XII$$

[0102] wherein R^6 and L^1 are as hereinbefore defined, for example under conditions that are known to those skilled in the art, which include reaction at between −10° C. and reflux temperature in the presence of a suitable base (e.g. triethylamine or pyridine) and, optionally, a reaction-inert solvent (e.g. THF or dichloromethane).

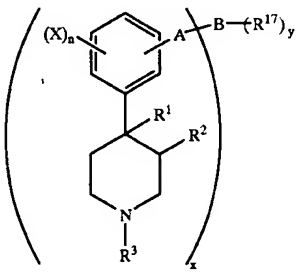
[0103] 15. Compounds of formula I in which A represents C_{1-4} alkyl and D represents $N(R^4)(^5)$ or $N(H)C(O)R^{10a}$ attached at the 1-, 2- or 3-C (relative to the benzene ring), wherein R^4, R^5 and R^{10a} are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which A represents C_{1-4} alkenylene unsaturated α,β-, β,γ- or γ,δ- (respectively) relative to the benzene ring and D represents H, with a compound of formula XI, as hereinbefore defined, or a compound of formula XIII,

$$NC—R^{10a} \qquad XIII$$

[0104] wherein R^{10a} is as hereinbefore defined, for example at between −10° C. and room temperature in the presence of a suitable mercury(II) salt (e.g. mercury(II) acetate, trifluoroacetate, nitrate, or perchlorate), optionally in the presence of a reaction-inert solvent (e.g. THF), and followed by in situ reduction of the mercury adduct by the addition of a suitable hydride-delivering agent (e.g. sodium borohydride), optionally in the presence of water.

[0105] 16. Compounds of formula I in which A represents C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH may be prepared by oxidation of a corresponding borane adduct of formula XIV,

XIV



[0106] wherein x is 1, 2-or 3, y is (as appropriate) (3-x) or 1, R^{17} is (as appropriate) H, halo, an alkyl, or a cycloalkyl group providing one or two bonds to boron (e.g. disiamyl or thexyl), A represents (as appropriate) C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and R^1, R^2, R^3, X and n are as hereinbefore defined, for example by reaction with a tertiary amine N-oxide (e.g. trimethylamine N-oxide) at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. THF or a THF/diglyme mixture).

[0107] The skilled person will appreciate that, in compounds of formula XIV, bonds between boron atoms and piperidine N-atoms may be present.

[0108] Compounds of formula XIV may be prepared by reaction of a corresponding compound of formula I in which A represents (as appropriate) C_{2-4} alkenylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents H with borane or a suitable derivative thereof (e.g. thexylborane, disiamylborane or 9-borabicyclo[3.3.1]nonane), for example at between −10° C. and room temperature in the presence of a suitable solvent (e.g. THF or a THF/diglyme mixture).

[0109] 17. Compounds of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH may be prepared by reaction of a corresponding compound of formula I in which A represents a C_{2-4} alkenylene group and D represents H with a suitable dihydroxylating reagent (e.g. sub-stoichiometric OsO_4 combined with 4-methylmorpholine N-oxide), for example at between 0° C. and reflux temperature in the presence of a reaction-inert solvent (e.g. a water/acetone mixture).

[0110] 18. Compounds of formula I in which A represents a single bond or a C_{1-2} alkylene group (as appropriate) and D represents C(O)H may be prepared by reaction of a corresponding of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH with a reagent that effects 1,2-diol oxidative cleavage (e.g. sodium periodate).

[0111] 19. Compounds of formula I in which D represents $C(=NR^{9a})R^8$ or $C(=NOR^{9b})R^8$, wherein R^8, R^{9a} and R^{9b} are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which D represents $C(O)R^8$ with a compound of formula XV,

$$H_2N—R^{9a} \qquad XV$$

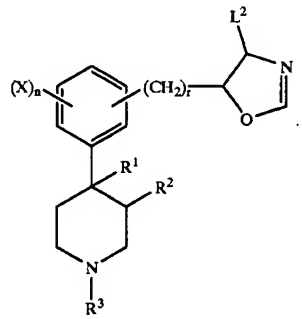
[0112] or a compound of formula XVI,

$$H_2N—OR^{9b} \qquad XVI$$

[0113] wherein R^{9a} and R^{9b} are as hereinbefore defined, for example under conditions that are known to those skilled in the are, which include reaction at between room and reflux temperature in the presence of a suitable solvent (e.g. a lower alkyl alcohol such as methanol or ethanol).

[0114] 20. Compounds of formula I in which A represents C_{1-4} alkylene substituted (α to D) with an OH group and D represents $N(H)CH_3$ (at the alkylene chain terminus) may be prepared by reduction of a corresponding compound of formula XVII,

XVII



[0115] wherein r is 0, 1 or 2, L^2 represents H or a group capable, when attached to a C_2 alkylene unit, of undergoing 1,2-elimination (relative to the L^2 group, e.g. an alkyl or aryl sulfoxide or sulfone), and R^1, R^2, R^3, X and n are as hereinbefore defined, for example, at between −10° C. and reflux temperature in the presence of a suitable reducing agent (e.g. lithium aluminium hydride) and a reaction-inert solvent (e.g. THF).

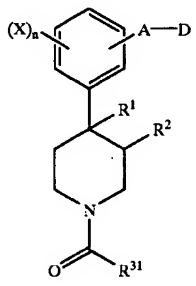
[0116] Compounds of formula XVII may be prepared by reaction of a corresponding compound of formula I in which A represents a single bond or C_{1-2} alkylene and D represents C(O)H with a compound of formula XVIII,

$$CN—CH_2—L^2 \qquad XVIII$$

[0117] wherein L^2 is as hereinbefore defined, for example at between 0° C. and reflux temperature in the presence of a suitable solvent (e.g. ethanol) and a catalytic quantity of a cyanide salt (e.g. sodium cyanide).

[0118] 21. Compounds of formula I wherein R^3 represents C_1 alkyl optionally substituted by C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified hereinbefore in respect to R^3), which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom via a CH_2 group, wherein Het^1 is as hereinbefore defined, may be prepared by reduction of a corresponding compound of formula XIX,

XIX



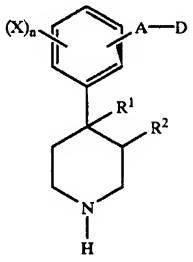
[0119] wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, —$CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^1)S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or

—W—A^1—$N(R^{12b})(R^{12c})$ and R^1, R^2, R^{11c}, R^{11d}, R^{12a} to R^{12c}, R^{13}, Het^1, n, p, W, X, A^1, A and D are as hereinbefore defined, using a suitable reducing agent (e.g. lithium aluminium hydride or a borane derivative), for example as described hereinbefore.

[0120] The skilled person will appreciate that this reduction may take place simultaneously with other reduction steps described herein (see, for example, processes 4, 9 and 16).

[0121] Compounds of formula XIX may be prepared by reaction of a corresponding compound of formula XX,

XX



[0122] wherein R^1, R^2, A, D, X and n are as hereinbefore defined with a compound of formula XXI,

$R^{31}CO_2H$ XXI

[0123] or a suitable (e.g. carboxylic acid) derivative thereof (e.g. an acid halide or anhydride), wherein R^{31} is as hereinbefore defined, using coupling conditions known to those skilled in the art.

[0124] Compounds of formulae XIX and XX may be prepared from appropriate precursors by analogy with methods; disclosed hereinbefore that describe the preparation of compounds of formula I.

[0125] 22. Compounds of formula I may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula VIII, as hereinbefore defined, under conditions that are well known to those skilled in the art, for example as described hereinbefore in respect of the production of compounds of formula VI.

[0126] 23. Compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined hereinbefore, is instead optionally substituted by R^{31}, wherein R^{31} is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XXII,

$R^{31}CHO$ XXII

[0127] wherein R^{31} is as hereinbefore defined, for example in the presence of a suitable reducing agent (e.g. sodium borohydride, sodium cyano-borohydride or sodium triacetoxyborohydride) and an appropriate solvent (e.g. methanol).

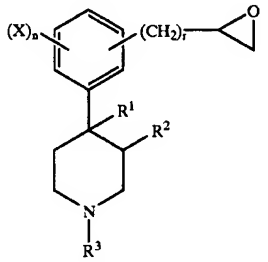
[0128] 24. Compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, —C(O)—A^1—$N(R^{12b})(R^{12c})$, —S(O)—A^1—N^{12b})(R^{12c}), or —$S(O)_2$—A^1—$N(R^{12b})(R^{12c})$ wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XXIII,

R^{3a}—Z XXIII

[0129] wherein R^{3a} represents R^3 as hereinbefore defined except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, —C(O)—A^1—$N(R^{12b})(R^{12c})$, —S(O)—A^1—$N(R^{12b})(R^{12c})$, or —$S(O)_2$—A^1—$N(R^{12b})(R^{12c})$ wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. THF).

[0130] 25. Compounds of formula I in which A represents C_{2-4} alkylene substituted (α to D) with an OH group and D represents $N(R^4)(R^5)$ (at the alkylene chain terminus), and R^4 and R^5 are as hereinbefore defined, may be prepared by reaction of a compound of formula XXIV,

XXIV

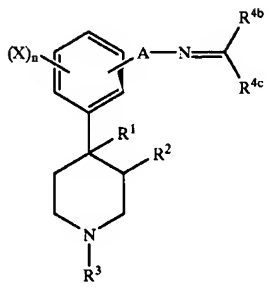


[0131] wherein R^1, R^2, R^3, X, n and r are as hereinbefore defined, with a compound of formula XI, as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e.g. potassium carbonate) and an appropriate solvent (e.g. N,N-dimethylformamide).

[0132] Compounds of formula XXIV may be prepared by dehydration of a corresponding compound of formula I in which A represents a C_{2-4} alkylene substituted (α to D) with an OH group and D represents OH (at the alkylene chain terminus) under conditions well known to those skilled in the art (e.g. by heating in concentrated sulfuric acid).

[0133] Compounds of formula XXIV may alternatively be prepared by epoxidation of a corresponding compound of formula I in which A represents a terminal C_{2-4} alkenylene group and D represents H under conditions well known to those skilled in the art (e.g. by reaction with meta-chloroperbenzoic acid).

[0134] 26. Compounds of formula I in which D represents $N(H)R^4$, wherein R^4 is as hereinbefore defined provided that it does not represent aryl, may be prepared by reduction of a corresponding compound of formula XXV,



XXV

[0135] wherein R^{4b} and R^{4c}, together with the carbonyl group to which they are attached, form a C_{1-6} alkanal, C_{3-6} alkanone, C_{3-8} cycloalkanone, phenyl(C_{1-4})alkanal or phenyl(C_{2-4})alkanone group, which five groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), and R^1, R^2, R^3, A, X and n are as hereinbefore defined (provided that the —N=C(R^{4b})R^{4c}) group is not directly attached to an unsaturated carbon atom), for example at between room and reflux temperature in the presence of a mild reducing agent (e.g. sodium borohydride) and a suitable solvent (e.g. a lower alkyl alcohol such as methanol or ethanol).

[0136] Compounds of formula XXV may be prepared by reaction of a corresponding compound of formula I in which D represents NH_2 with a compound of formula XXVI,

$R^{4b}C(O)R^{4c}$ XXXVI

[0137] wherein R^{4b} and R^{4c} are as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. a lower alkyl alcohol such as methanol or ethanol) and optionally in the presence of a Lewis-acidic catalyst.

[0138] 27. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents N(R^4)(R^5) (attached to a CH_2 group), wherein R^4 and R^5 are as hereinbefore defined, may be prepared by reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents C(O)N(R^4)(R^5), for example in the presence of a suitable is reducing agent (e.g. lithium aluminium hydride or a borane derivative) and a reaction-inert solvent (e.g. THF).

[0139] Compounds of formulae II, III, VIII, X, R^{7a}OH, XI, XII, XIII, XV, XVI, XVIII, XXI, XXII, XXIII, XXVI, and derivatives thereof, when not commercially available or not subsequently described, may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

[0140] Substituents on alkyl, heterocyclic and aryl groups in the above-mentioned compounds may also be introduced, removed and interconverted, using techniques which are well known to those skilled in the art. For example, nitro may be reduced to amino, OH may be alkylated to give alkoxy, alkoxy may be hydrolysed to OH, alkenes may be hydrogenated to alkanes, halo may be hydrogenated to H, etc.

[0141] In some cases it is possible to introduce further substituents into the compounds of formula I directly. For example, chlorination of the phenyl group of compounds of formula I, may be performed by reaction with a solution of chlorine in acetic acid.

[0142] The skilled person will also appreciate that other various standard substituent or functional group interconversions and transformations within certain compounds of formula I will provide other compounds of formula I.

[0143] The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

[0144] It will be appreciated by those skilled in the art that, in the course of carrying out the processes described above, the functional groups of intermediate compounds may need to be protected by protecting groups.

[0145] Functional groups which it is desirable to protect include oxo, OH, amino and carboxylic acid. Suitable protective groups for oxo include acetals, ketals (e.g. ethylene ketals) and dithianes. Suitable protective groups for OH include trialkylsilyl and diarylalkylsilyl groups (e.g. tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protective groups for amino include tert-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl.

[0146] Suitable protective groups for carboxylic acid include C_{1-6} alkyl or benzyl esters. Suitable protective groups for terminal alkynes include trialkylsilyl and diarylalkylsilyl groups (e.g. tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl).

[0147] The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

[0148] Protective groups may be removed in accordance with techniques which are well known to those skilled in the art.

[0149] The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2nd edition, TW Greene & PGM Wutz, Wiley-Interscience (1991).

[0150] Persons skilled in the art will also appreciate that, in order to obtain compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This will depend inter alia on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the

type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis. The procedures may be adapted as appropriate to the reactants, reagents and other reaction parameters in a manner that will be evident to the skilled person by reference to standard textbooks and to the examples provided hereinafter.

[0151] It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be admtinistered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of formula I may act as prodrugs of other compounds of formula I.

[0152] It will be further appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described in 'Design of Prodrugs' by H. Bundgaard, Elsevier, 1985 (the disclosure in which document is hereby incorporated by reference), may be placed on appropriate functionalities, when such functionalities are present within compounds of formula I.

[0153] All protected derivatives, and prodrugs, of compounds of formula I are included within the scope of the invention.

[0154] Pharmaceutically acceptable acid addition salts of the compounds of formula I which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt may then be isolated either by filtration of by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula I with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

[0155] The above procedures may be adapted as appropriate to the particular reactants and groups involved and other variants will be evident to the skilled chemist by reference to standard textbooks and to the examples provided hereafter to enable all of the compounds of formula I to be prepared.

[0156] The compounds of the invention are useful because they possess pharmacological activity in animals, especially mammals including humans. They are therefore indicated as pharmaceuticals and, in particular, for use as animal medicaments.

[0157] According to a further aspect of the invention there is provided the compounds of the invention for use as medicaments, such as pharmaceuticals and animal medicaments.

[0158] By the term "treatment", we include both therapeutic (curative) or prophylactic treatment.

[0159] In particular, the compounds of the invention have been found to be useful in the treatment of diseases mediated via opiate receptors, which diseases include irritable bowel syndrome; constipation; nausea; vomiting; pruritus; and conditions characterised by pruritus as a symptom.

[0160] Thus, according to a further aspect of the invention there is provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a disease mediated via an opiate receptor. There is further provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of irritable bowel syndrome; constipation; nausea; vomiting; pruritus or a medical condition characterised by pruritus as a symptom.

[0161] The compounds of the invention are thus expected to be useful for the curative or prophylactic treatment of pruritic dermatoses including allergic dermatitis and atopy in animals and humans. Other diseases and conditions which may be mentioned include contact dermatitis, psoriasis, eczema and insect bites.

[0162] Thus, the invention provides a method of treating or preventing a disease mediated via an opiate receptor. There is further provided a method of treating irritable bowel syndrome; constipation; nausea; vomiting; pruritus or a medical condition characterised by pruritus as a symptom in an animal (e.g. a mammal), which comprises administering a therapeutically effective amount of a compound of the invention to an animal in need of such treatment.

[0163] The compounds of the invention will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses (see below).

[0164] While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical, or veterinary, formulation comprising a pharmaceutically, or veterinarily, acceptable carrier, diluent or excipient and a compound of the invention. The carrier, diluent or excipient may be selected with due regard to the intended route of administration and standard pharmaceutical, and/or veterinary, practice. Pharmaceutical compositions comprising the compounds of the invention may contain from 0.1 percent by weight to 90.0 percent by weight of the active ingredient.

[0165] The methods by which the compounds may be administered for veterinary use include oral administration by capsule, bolus, tablet or drench, topical administration as an ointment, a pour-on, spot-on, dip, spray, mousse, shampoo, collar or powder formulation or, alternatively, they can be administered by injection (e.g. subcutaneously, intramuscularly or intravenously), or as an implant. Such formulations may be prepared in a conventional manner in accordance with standard veterinary practice.

[0166] The formulations will vary with regard to the weight of active compound contained therein, depending on the species of animal to be treated, the severity and type of infection and the body weight of the animal. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10 mg per kg.

[0167] The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discreet units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

[0168] In any event, the veterinary practitioner, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which may vary with the species, age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[0169] For veterinary use, the compounds of the invention are of particular value for treating pruritus in domestic animals such as cats and dogs and in horses.

[0170] As an alternative for treating animals, the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

[0171] For human use, the compounds are administered as a pharmaceutical formulation containing the active ingredient together with a pharmaceutically acceptable diluent or carrier. Such compositions include conventional tablet, capsule and ointment preparations which are formulated in accordance with standard pharmaceutical practice.

[0172] Compounds of the invention may be administered either alone or in combination with one or more agents used in the treatment or prophylaxis of disease or in the reduction or suppression of symptoms. Examples of such agents (which are provided by way of illustration and should not be construed as limiting) include antiparasitics, e.g. fipronil, lufenuron, imidacloprid, avermectins (e.g. abamectin, ivermectin, doramectin), milbemycins, organophosphates, pyrethroids; antihistamines, e.g. chlorpheniramine, trimeprazine, diphenhydramine, doxylamine; antifungals, e.g. fluconazole, ketoconazole, itraconazole, griseofulvin, amphotericin B; antibacterals, e.g. enroflaxacin, marbofloxacin, ampicillin, amoxycillin; anti-inflammatories e.g. prednisolone, betamethasone, dexamethasone, carprofen, ketoprofen; dietary supplements, e.g. gamma-linoleic acid; and emollients. Therefore, the invention further provides a product containing a compound of the invention and a compound from the above list as a combined preparation for simultaneous, separate or sequential use in the treatment of diseases mediated via opiate receptors.

[0173] The skilled person will also appreciate that compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

[0174] Thus, according to a further aspect of the invention there is provided a pharmaceutical, or veterinary, formulation including a compound of the invention in admixture with a pharmaceutically, or veterinarily, acceptable adjuvant, diluent or carrier.

[0175] Compounds of the invention may also have the advantage that, in the treatment of human and/or animal patients, they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or they may have other useful pharmacological properties over, compounds known in the prior art.

[0176] The biological activities of the compounds of the present invention were determined by the following test method.

[0177] Biological Test

[0178] Compounds of the present invention have been found to display activity in binding assays selective for the mu opioid receptor in dog brain. The assays were conducted by the following procedure.

[0179] Laboratory bred beagles were used as a source of dog brain tissue. Animals were euthanised, their brains removed and the cerebellum discarded. The remaining brain tissue was sectioned into small pieces approximately 3 g in weight and homogenised in 50 mM Tris pH 7.4 buffer at 4° C. using a Kinematica Polytron™ tissue homogeniser. The resulting homogenate was centrifuged at 48,400× g for 10 minutes and the supernatant discarded. The pellet was resuspended in Tris buffer and incubated at 37° C. for 10 minutes. Centrifugation, resuspension and incubation steps were repeated twice more, and the final pellet was resuspended in Tris buffer and stored at −80° C. Membrane material prepared in this manner could be stored for up to four weeks prior to use.

[0180] For mu assays, increasing concentrations of experimental compound, (5×10^{-12} to 10^{-5} M), Tris buffer and ^{3}H ligand, ([D-Ala^2,N-Me-Phe^4,Gly-ol^5]-Enkephalin, DAMGO), were combined in polystyrene tubes. The reaction was initiated by the addition of tissue, and the mixture was incubated at room temperature for 90 minutes. The reaction was terminated by rapid filtration using a Brandel Cell Harvester™ through Betaplate™ GF/A glass fibre filters pre-soaked in 50 mM Tris pH 7.4, 0.1% polyethylenimine buffer. The filters were then washed three times with 0.5 mL ice-cold Tris pH 7.4 buffer. Washed filters were placed in bags and Starscint™ scintillant added. Bags containing the filters and scintillant were heat sealed and counted by a Betaplate™ 1204 beta counter.

[0181] Duplicate samples were run for each experimental compound and the data generated was analysed using IC_{50} analysis software in Graphpad Prism. Ki values were calculated using Graphpad Prism according to the following formula:

$$Ki=IC_{50}/1+[^3\text{H ligand}]KD$$

[0182] where IC_{50} is the concentration at which 50% of the ^{3}H ligand is displaced by the test compound and K_D is the dissociation constant for the ^{3}H ligand at the receptor site.

[0183] The invention is illustrated by the following Preparations and Examples in which the following abbreviations may be used:

[0184] APCI=atmospheric pressure chemical ionisation

[0185] br (in relation to NMR)=broad

[0186] DMF=N,N-dimethylformamide

[0187] DMSO=dimethylsulfoxide

[0188] d (in relation to time)=day

[0189] d (in relation to NMR)=doublet

[0190] dd (in relation to NMR)=doublet of doublets

[0191] EtOAc=ethyl acetate

[0192] EtOH=ethanol

[0193] h=hour(s)

[0194] m (in relation to NMR)=multiplet

[0195] MeOH=methanol

[0196] min=minute

[0197] q (in relation to NMR)=quartet

[0198] s (in relation to NMR)=singlet

[0199] t (in relation-to NMR)=triplet

[0200] THF=tetrahydrofuiran

[0201] When reverse phase HPLC is mentioned in the text the following 2 sets of conditions were employed.

[0202] Condition 1: A Phenomenex Magellenl™ column, 150x21 mm, packed with 5 m C_{18} silica, eluting with a gradient of acetonitrile: 0.1 M aqueous ammonium acetate (30:70 to 95:5 over 10 mins, flow rate 20 mL per minute).

[0203] Condition 2: A Dynamax™ column, 42x250 mm, packed with 8μ C_{18} silica, eluting with acetonitrile : 0.1 M aqueous ammonium acetate (30:70) at 45 mL per minute.

[0204] In both cases, combination and evaporation of appropriate fractions, determined by analytical HPLC, provided the desired compounds as acetate salts.

[0205] Analytical HPLC conditions used to highlight appropriate fractions were Phenomenex Magellan™ column, 4.6x150 mm, packed with 5μ C_{18} silica, eluting with a gradient of acetonitrile : 0.1 M aqueous heptanesulfonic acid (10:90 to 90:10 over 30 min, followed by a further 10 min at 90:10) at 1 mL per minute. Column oven temperature was 40° C., and ultraviolet detection of components was made at 220 nM.

[0206] When column chromatography is referred to this usually refers to a glass column packed with silica gel (40-63 μm). Pressure of ~165 kPa is generally applied and the ratio of crude product: silica gel required for purification is typically 50:1. Alternatively, an Isolute™ SPE (solid phase extraction) column or Waters Sep-Pak™ cartridge packed with silica gel may be used under atmospheric pressure. The ratio of crude product to silica gel required for purification is typically 100:1.

[0207] The hydrochloride salt may be made by methods commonly known to those skilled in the art of synthetic chemistry. Typically, to a solution of free base in dichloromethane (1 g : 100 mL) was added ethereal hydrochloric acid (1.0 M, 1.2 equivalent), the excess solvent was decanted off and the remaining precipitate was washed three times with ether and then dried in vacuo.

[0208] Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance (NMR) spectral data were obtained using a Varian Unity 300 or 400 spectrometer, the observed chemical shifts (δ) being consistent with the proposed structures. Mass spectral (MS) data were obtained on a Fisons Instruments Trio 1000, or a Fisons Instruments Trio 1000 APCI, or a Finnigan Navigator MS, or a Micromass Platform LC spectrometer. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. HPLC means high performance liquid chromatography. Room temperature means 20 to 25° C.

EXAMPLES

Example 1

1-Hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine

[0209] A solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 1, 500 mg, 1.19 mmol) in 1-methyl-2-pyrrolidinone (2.5 mL) was added to a flask containing potassium cyanide (155 mg, 2.38 mmol). The solution was de-oxygenated by evacuating and flushing with nitrogen three times. Catalytic quantities of palladium(II) acetate and 1,1 '-bis(diphenylphosphino)ferrocene were added and the reaction mixture was warmed to 60° C., at which temperature it was stirred for 3 hours. The reaction mixture was cooled to room temperature and poured into saturated aqueous sodium hydrogencarbonate solution (50 mL). The product was extracted into ethyl acetate (3x30 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (15 g) eluted with a gradient of ethyl acetate:hexane:0.880 ammonia (20:79:1 to 50:49:1) to give the title compound as an oil (346 mg).

[0210] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 7.35-7.6 (m, 41).

[0211] MS (electrospray): M/Z (MH^+) 299.2; $C_{20}H_{30}N_2$+H requires 299.2.

Example 2

1-Hexyl-3,4-dimethyl-4-(3-amidophenyl)piperidine

[0212] A mixture of polyphosphoric acid (160 mg) and 1-hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine (Example 1, 19 mg, 0.064 mmol) was heated at 115° C. for one hour. The reaction mixture was then cooled to room temperature and diluted with iced water (0.4 mL). Aqueous sodium hydroxide solution (2 N) was added until the pH was 7. The mixture was extracted with ethyl acetate (3x10 mL). The combined organics were dried (Na_2SO_4) and the solvent evaporated in vacuo to give a white solid. Purification by column chromatography on silica gel (1 g) eluted with ethyl acetate : ethanol : 0.880 ammonia (89:10:1) gave the product as a white solid (6 mg).

[0213] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 7.35 (t, 1H), 7.45 (d, 1H), 7.55 (d, 1H), 7.8 (s, 1H).

[0214] MS (electrospray): M/Z (MH^+) 317.3; $C_{20}H_{32}N_2O$+H requires 317.3.

Example 3

1-Hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine

[0215] To a stirred solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine (Preparation

1, 500 mg, 1.19 mmol) in anhydrous N,N-dimethylformnamide (6 mL) was added triethylamine (1.7 mL, 12.2 mmol) and anhydrous methanol (1.0 mL, 24.7 mmol). The solution was de-oxygenated by evacuating and flushing with nitrogen five times. Palladium(II) acetate (27 mg, 0.12 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (67 mg, 0.12 mmol) were added and the mixture was de-oxygenated again, using the same procedure as before. Carbon monoxide gas was bubbled through the mixture for 5 minutes and it was then stirred under an atmosphere of carbon monoxide and heated at 120° C. overnight. The solvent was removed in vacuo to give a brown oil (0.7 g) which was purified by column chromatography on silica gel (35 g) eluted with a gradient of ethyl acetate:hexane:0.880 ammonia (10:190:1 to 10:90:1 to 25:75:1). This gave the title compound as a yellow oil (250 mg).

[0216] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m containing s, 9H), 1.4-1.55 (m, 2H), 1.7 (m, 1H), 2.1 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 3.9 (s, 3H), 7.35 (t, 1H), 7.5 (d, 1H), 7.85 (d, 1H), 8.0 (s, 1H).

[0217] MS (APCI): M/Z (MH^+) 332.4; $C_{21}H_{33}NO_2$+H requires 332.3.

Example 4

1-Hexyl-3,4-dimethyl-4-(3-(N-isopropyl)amidophenyl)-piperidine

[0218] In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 40 mg, 0.12 mmol) and isopropylamine (5 mL, 59 mmol) were heated together at 150° C. for two days. The reaction mixture was then cooled to room temperature and excess amine was removed by evaporation in vacuo. The residue was purified by column chromatography on silica gel (5 g) eluted with ethyl acetate:ethanol:0.880 ammonia (50:49:1) to give the title compound as an oil (32 mg).

[0219] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 15H), 1.4-1.55 (m, 2H), 1.65 (m, 1H); 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 4.3 (m, 1H) 7.3-7.5 (m, 3H), 7.75 (s, 1H).

[0220] MS (electrospray): M/Z (MH^+) 359.3; $C_{23}H_{38}N_2O$+H requires 359.3.

Example 5

1-Hexyl-3,4-dimethyl-4-(3-(N-butyl)amidophenyl)-piperidine

[0221] In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and n-butylamine (4 mL, 40.5 mmol) were heated together at 140° C. for two days. The reaction mixture was then cooled to room temperature and excess amine was removed by evaporation in vacuo. The residue was purified by column chromatography on silica gel (5 g) eluted with ethyl acetate:hexane:0.880 ammonia (40:49:1) to give the title compound as an oil (20 mg).

[0222] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 0.95 (t, 3H), 1.2-1.8 (m, 16H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 3.45 (m, 2H), 7.3-7.55 (m, 3H), 7.75 (s, 1H).

[0223] MS (electrospray): M/Z (MH^+) 373.3; $C_{24}H_{40}N_2O$+H requires 373.3.

Example 6

1-Hexyl-3,4-dimethyl-4-(3-(N-propyl)amidophenyl)-piperidine

[0224] In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and n-propylamine (4 mL, 94 mmol) were heated together at 140° C. for two days. The reaction mixture was then cooled to room temperature and excess amine was removed by evaporation in vacuo. The residue was purified by column chromatography on silica gel (5 g) eluted with ethyl acetate: ethanol: 0.880 ammonia (50:49:1) to give the title compound as an oil (3.5 mg).

[0225] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.0 (t, 3H), 1.25-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6-1.75 (m, 3H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.45 (m, 2H), 7.3-7.5 (m, 3H), 7.75 (s, 1H).

[0226] MS (electrospray): M/Z (MH^+) 359.3; $C_{23}H_{38}N_2O$+H requires 359.3.

Example 7

1-Hexyl-3,4-dimethyl-4-(3-(N-benzyl)amidophenyl)-piperidine

[0227] In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and benzylamine (3 mL, 27.5 mmol) were heated together at 100° C. for 76 hours. The reaction mixture was cooled to room temperature, concentrated and the residue purified by column chromatography on silica gel eluted with a gradient of hexane:ethyl acetate (20:80 to 50:50). The title compound was obtained as a pale oil (13 mg).

[0228] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (t, 3H), 1.2-1.4 (m, 9H), 1.6-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 4.65 (m, 2H), 7.3-7.4 (m, 6H), 7.45 (d, 1H), 7.55 (d, 1H), 7.8 (s, 1H). MS (electrospray): M/Z (MH^+) 407.3; $C_{27}H_{38}N_2O$+H requires 407.3.

Example 8

1-Hexyl-3,4-dimethyl-4-(3-(N-ethyl)amidophenyl)-piperidine

[0229] In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and ethylamine (3 mL, 45.8 mmol) were heated together at 1 00C for 60 hours. The ethylamine was found to be evaporating, thus the reaction mixture was transferred to a sealed bomb and heated at 100° C. and 690 kPa for a further 16 hours. The reaction mixture was cooled to room temperature, concentrated and then purified by column chromatography on silica gel eluted with a gradient of hexane:ethyl acetate (20:80 to 50:50). The title compound was obtained as a pale oil (11 mg).

[0230] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 12H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05

(m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 21), 2.85 (m, 1H), 3.5 (m, 2H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

[0231] MS (thermospray): M/Z (MH^+) 345.1 $C_{22}H_{36}N_2O$+H requires 345.3.

Example 9

1-Hexyl-3,4-dimethyl-4-(3-(N-isobutyl)amidophenyl)-piperidine

[0232] The title compound was prepared by the method of Example 7, substituting benzylamine with isobutylamine (3 mL, 30.18 mmol). This gave the title compound as a pale oil (9 mg).

[0233] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (t, 3H), 1.0 (d, 6H), 1.2-1.35 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 1.9 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.3, (t, 2H), 7.35 (t, 1H), 7.45 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

[0234] MS (electrospray): M/Z (MH^+) 373.3; $C_{24}H_{40}N_2O$+H requires 373.3.

Example 10

1-Hexyl-3,4-dimethyl-4-{3-[N-(2-methoxyethyl)]-amidophenyl}piperidine

[0235] In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and 2-methoxyethylamine (3 mL, 34.5 mmol) were heated together at 130° C. for 120 hours. The reaction mixture was cooled to room temperature, concentrated and purified by column chromatography on silica gel eluted with a gradient of hexane:ethyl acetate:0.880 ammonia gradient (10:89:1 to 49:50:1). The gave the title compound as a pale oil (8 mg).

[0236] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.3-3.7 (m, 7H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

[0237] MS (APCI): M/Z (MH^+) 374.5; $C_{23}H_{38}N_2O_2$+H requires 374.3.

Example 11

1-Hexyl-3,4-dimethyl-4-(3-(N-methyl)amidophenyl)-piperidine

[0238] To a suspension of anhydrous methylamine hydrochloride (17 mg, 0.25 mmol) in anhydrous toluene (0.5 mL) stirred under nitrogen and cooled in an ice bath was added a solution of trimethylaluminium (2.0 M in toluene, 0.12 mL, 0.24 mmol). The mixture was allowed to warm to room temperature while stirring for 4 hours, then it was treated with a solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 40 mg, 0.12 mmol) in anhydrous toluene (1.5 mL). The resulting mixture was heated at reflux overnight, then quenched with dilute hydrochloric acid (10 mL of 2 N) and extracted with diethyl ether (10 mL). The aqueous phase was basified to pH 13 with aqueous sodium hydroxide solution (2 N) and extracted with dichloromethane (3×20 mL). The combined dichloromethane extracts were dried (Na_2SO_4) and concentrated in vacuo to give an orange oil (31 mg) which was purified by column chromatography on silica gel (1.2 g) eluted with ethyl acetate:hexane:0.880 ammonia (50:50:1). This gave the title compound as a colourless residue (17 mg).

[0239] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 21), 1.65 (m,. 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.0 (d, 3H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

[0240] MS (APCI) M/Z (MH^+) 331.1; $C_{21}H_{34}N_2O$+H requires 331.3.

Example 12

1-Hexyl-3,4-dimethyl-4-(3-(N,N-dimethyl)amidophenyl)-piperidine

[0241] The title compound was prepared as for Example 11 except using anhydrous dimethylamine hydrochloride (20 mg, 0.25 mmol) in place of methylamine hydrochloride. This gave a pale yellow oil (38 mg).

[0242] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 2.95 (br s, 3H), 3.1 (br s, 3H), 7.15-7.25 (m, 1H), 7.25-7.4 (m, 3H).

[0243] MS (thermospray): M/Z (MH^+) 345.2; $C_{22}H_{36}N_2O$+H requires 345.3.

Example 13

1-Hexyl-3,4-dimethyl-4-(3-(N,N-diethyl)amidophenyl)-piperidine

[0244] To a suspension of anhydrous diethylamine hydrochloride (30 mg, 0.27 mmol) in anhydrous toluene (0.5 mL) stirred under nitrogen and cooled in an ice bath was added a solution of trimethylaluminium (2.0 M in toluene, 0.14 mL, 0.28 mmol). The mixture was allowed to warm to room temperature while stirring for 2 hours, then it was treated with a solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 44 mg, 0.13 mmol) in anhydrous toluene (1 mL). The resulting mixture was heated at reflux for 2½ days, then quenched with dilute hydrochloric acid (10 mL of 2 N) and extracted with diethyl ether (10 mL). The aqueous phase was basified to pH 13 with aqueous sodium hydroxide solution (2 N) and extracted with dichloromethane (3×20 mL). The combined dichloromethane extracts were dried (Na_2SO_4) and concentrated in vacuo to give an orange oil (52 mg) which was purified by column chromatography on silica gel (1.5 g) eluted with a gradient of ethyl acetate:hexane:0.880 ammonia (10:90:1 to 20:40:1). This gave the title compound as a yellow oil (34 mg).

[0245] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.0-1.4 (m, 15H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.25 (br m, 2H), 3.55 (br m, 2H), 7.1-7.2 (m, 1H), 7.2-7.35 (m, 3H).

[0246] MS (APCI): M/Z (MH^+) 373.1; $C_{24}H_{40}N_2O$+H requires 373.3.

Example 14

1-Hexyl-3,4-dimethyl-4-(3-(N-tert-butyl)amidophenyl)-piperidine

[0247] A solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine (Example 3, 40 mg, 0.12 mmol)

in dilute hydrochloric acid (5 mL of 2 N) was heated at reflux overnight. The solvent was removed in vacuo and the residue was taken up in methanol and re-concentrated in vacuo to give a brown oil (40 mg) which was dissolved in dichloromethane (1 mL) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (25 mg, 0.13 mmol), N-methylmorpholine (27 μL; 0.25 mmol) and tert-butylamine (14 μL, 0.13 mmol). The resulting mixture was stirred at room temperature overnight, then poured into saturated aqueous sodium hydrogencarbonate solution (5 mL.) and extracted with dichloromethane (3×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a brown residue which was purified by column chromatography on silica gel (2.5 g) eluted with a gradient of ethyl acetate:hexane:0.880 ammonia (5:95:1 to 10:90:1 to 20:80:1 to 30:70:1). This gave the title compound as a colourless residue (10 mg).

[0248] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 1H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 7.3-7.45 (m, 3H), 7.75 (s, 1H).

[0249] MS (APCI): M/Z (MH^+) 373.1; $C_{24}H_{40}N_2O$+H requires 373.3.

Example 15

1-Benzyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine

[0250] A stirred solution of 1-benzyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 2, 506 mg, 1.18 mmol), triethylamine (1.6 mL, 11.8 mmol) and anhydrous methanol (1.9 mL, 46.8 mmol) in anhydrous N,N-dimethylformamide (6 mL) was de-oxygenated by evacuating and flushing with nitrogen five times. Palladium(II) acetate (30 mg, 0.13 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (63 mg, 0.11 mmol) were added and the mixture was again de-oxygenated, using the same method as before. Carbon monoxide gas was bubbled through the mixture for ca 5 minutes and it was subsequently heated at 80° C. under an atmosphere of carbon monoxide overnight. The mixture was then poured into water (100 mL) and extracted with diethyl ether (3×100 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give an orange oil (250 mg). A black residue remaining in the reaction flask, insoluble in diethyl ether, was dissolved in dichloromethane and transferred to the separating funnel containing the aqueous layer and this was re-extracted with dichloromethane (3×50 mL). The combined organics were filtered through Celite® to remove residual palladium, dried (Na_2SO_4) and concentrated in vacuo to give a brown oil (270 mg). The combined oils were purified by silica (25 g) column chromatography eluting with a gradient of hexane:ethyl acetate : 0.880 ammonia (140:10:1 to 90:10:1) to give the title compound as a colourless oil (335 mg).

[0251] NMR ($CDCl_3$): 0.75 (d, 3H), 1.35 (s, 3H), 1.65 (m, 1H), 2.05 (m, 1H), 2.3-2.5 (m, 2H), 2.5-2.65 (m, 2H), 2.85 (m, 1H), 3.45 (d, 1H), 3.6 (d, 1H), 3.9 (s, 3H), 7.2-7.4 (m, 6H), 7.5 (d, 1H), 7.85 (d, 1H), 8.0 (s, 1H).

[0252] MS (thermospray):M/Z (MH^+) 338.2; $C_{22}H_{27}NO_2$+H requires 338.2.

Example 16

1-Benzyl-3,4-dimethyl-4-(3-(N-ethyl)amidophenyl)-piperidine

[0253] A stirred suspension of ethylamnine hydrochloride (880 mg, 10.8 mmol) in anhydrous toluene (10 mL) was de-oxygenated by evacuating and flushing with nitrogen three times. Stirring under nitrogen it was cooled in an ice bath and treated with trimethylaluminium solution (2.0 M in toluene, 5.4 mL, 10.8 mmol) via syringe. The mixture was allowed to warm to room temperature while stirring for 1¼ hours. A solution of 1-benzyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 15, 1.81 g, 5.36 mmol) in anhydrous toluene (20 mL) was added via syringe and the reaction mixture was heated at reflux overnight. After it had cooled, aqueous hydrochloric acid (100 mL of 2 N) was added and the mixture was extracted with diethyl ether (100 mL). The organic extract was back-washed with aqueous hydrochloric acid (50 mL of 2 N). The combined aqueous phases were basified to pH 13 with aqueous sodium hydroxide solution (2 it and then extracted with dichloromethane (300 mL followed by 2×100 mL). The combined dichloromethane extracts were washed with water (150 mL) followed by saturated aqueous sodium chloride solution (150 mL), dried (Na_2SO_4) and concentrated in vacuo to give a brown oil (2.0 g). Purification by silica (100 g) column chromatography eluting with a gradient of ethyl acetate:hexane:0.880 ammonia (20:80:1 to 30:70:1 to 40:60:1) gave the title compound as a cream foam (805 mg).

[0254] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 1.25 (t, 3H), 1.35 (s, 3H), 1.65 (m, 1H), 2.05 (m, 1H), 2.35-2.45 (m, 2H), 2.5-2.6 (m, 2H), 2.85 (m, 1H), 3.4-3.55 (m, 3H), 3.6 (d, 1H), 7.2-7.35 (m, 6H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

[0255] MS (APCI): M/Z (MH^+) 351.3; $C_{23}H_{30}N_2O$+H requires 351.2.

Example 17

1-(2-Phenoxyethyl)-3,4-dimethyl-4-(3-(N-ethyl)-amidophenyl)piperidine

[0256] A stirred mixture of 3,4-dimethyl-4-(3-(N-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol), 2-bromoethyl phenyl ether (42 mg, 0.20 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous N,N-dimethylformamide (1 mL) was heated at 100° C. for 2 hours. The solvent was then removed in vacuo to give a brown oil which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2:MeOH (25:1), to give the title compound as a yellow oil (55 mg).

[0257] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 1.25 (t, 3H), 1.35 (s, 3H), 1.65 (m, 1H), 2.05 (m, 1H), 2.35 (m, 1H), 2.55 (m, 1H), 2.6-2.8 (m, 3H), 2.8-2.95 (m, 2H), 3.5 (m, 2H), 4.1 (m, 2H), 6.9-7.0 (m, 3H), 7.3 (m, 2H), 7.35 (m, 1H), 7.4 (m, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

[0258] MS (thermospray): M/Z (MH^+) 381.2; $C_{24}H_{32}N_2O_2$+H requires 381.3.

Example 18

1-(5-Methylhexyl)-3,4-dimethyl-4-(3-(N-ethyl)-amidophenyl)piperidine

[0259] A stirred mixture of 3,4-dimethyl-4-(3-(N-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol),

1-bromo-5-methylhexane (37 mg, 0.20 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous N,N-dimethylformamide (1 mL) was heated at 100° C. for 2½ hours. The solvent was then removed in vacuo to give a brown oil which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2:MeOH (25:1), to give the title compound as a yellow oil (58 mg).

[0260] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.85 (d, 6H), 1.15 (m, 2H), 1.2-1.35 (m, 8H), 1.35-1.6 (m, 3H), 1.65 (m, 1H), 2.05 (m, 11H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 3.5 (m, 2H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

[0261] MS (thermospray): M/Z (MH^+) 359.5; $C_{23}H_{38}N_2O$+H requires 359.3.

Example 19

1-(3-Phenylpropyl)-3,4-dimethyl-4-(3-(N-ethyl)-amidophenyl)piperidine

[0262] A stirred mixture of 3,4-dimethyl-4-(3-(N-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol), 1-bromo-3-phenylpropane (32 μL, 0.21 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous N,N-dimethylformamide (1 mL) was heated at 100° C. for 2 hours. The solvent was then removed in vacuo to give a brown oil which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2:MeOH (25:1), followed by further purification by column chromatography on silica gel (4 g) eluted with a gradient of CH_2Cl_2 MeOH (50:1 to 50:2). This gave the title compound as a yellow oil (55 mg).

[0263] NMR ($CDCl_3$, selected, data): 0.75 (d, 3H), 1.25 (t, 3H), 1.3 (s, 3H), 1.65 (m, 1H), 1.8 (m, 2H), 2.05 (m, 1H), 2.25-2.45 (m, 4H), 2.45-2.7 (m, 4H), 2.85 (m, 1H), 3.5 (m, 2H), 7.15-7.2 (m, 3H), 7.25 (m, 2H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 11), 7.75 (s, 1H).

[0264] MS (thermospray): M/Z (MH^+) 379.0; $C_{25}H_{34}N_2O$+H requires 379.3.

Example 20

1-(5-Cyanopentyl)-3,4-dimethyl-4-(3-(N-ethyl)-amidophenyl)piperidine

[0265] A stirred mixture of 3,4-dimethyl-4-(3-(N-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol), 6-bromohexanenitrile (28 μL, 0.20 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous N,N-dimethylformamide (1 mL) was heated at 100° C. for 4 hours. The solvent was then removed in vacuo to give a brown oil which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2:MeOH (25:1), to give a yellow oil (82 mg), followed by further purification by column chromatography on silica gel (4 g) eluted with a gradient of CH_2Cl_2:MeOH (50:1 to 50:2). This gave the title compound as a yellow oil (54 mg).

[0266] NMR ($CDCl_3$, selected data): 0.8 (d, 3H), 1.25 (t, 3H), 1.35 (s, 3H), 1.5 (m, 2H), 1.55-1.8 (m, 5H), 2.15 (m, 1H), 2.35 (t, 2H), 2.4-2.6 (m, 4H), 2.6-2.75 (m, 2H), 2.95 (m, 1H), 3.5 (m, 2H), 7.3-7.45 (m, 2H), 7.5 (d, 1H), 7.75 (s, 1H).

[0267] MS (thermospray): M/Z (MH^+) 356.4; $C_{22}H_{33}N_3O$+H requires 356.3.

Example 21

1-Hexyl-3,4-dimethyl-4-(3-aminomethylphenyl)piperidine

[0268] To a stirred solution of 1-hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine (Example 1, 800 mg, 2.68 mmol) in anhydrous tetrahydrofuran (40 mL) at 0° C. under nitrogen was added lithium aluminium hydride (1.0 M in tetrahydrofuran, 4.0 mL, 4.0 mmol). The reaction mixture was allowed to warm to room temperature, before being heated to 37° C. for 30 minutes. Subsequently, diethyl ether (50 mL), then aqueous sodium hydroxide (0.3 mL, 15% w/v solution) and finally water (0.45 mL) were added. The white solid formed was filtered off. The filtrate was washed with saturated aqueous sodium hydrogencarbonate solution (2×50 mL). The aqueous phases were back-extracted with diethyl ether (50 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo to give the title compound as an oil (770 mg).

[0269] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 3.85 (s, 2H), 7.1-7.35 (m, 4H).

[0270] MS (APCI): M/Z (MH^+) 303.4; $C_{20}H_{34}N_2$+H requires 303.3.

Example 22

1-Hexyl-3,4-dimethyl-4-(3-(N-methoxycarbonyl)aminomethylphenyl)piperidine

[0271] To a stirred solution of 1-hexyl-3,4-dimethyl-4-(3-aminomethylphenyl)-piperidine (Example 21, 100 mg, 0.33 mmol) in pyridine (2 mL, dried over basic alumina) at 0° C. under nitrogen was added methyl chloroformate (40 μL, 0.52 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. Subsequently, ice was added followed by aqueous sodium hydroxide (5 N solution) to give a pH of 11. The mixture was extracted with diethyl ether (3×25 mL). The combined organic phases was dried ($MgSO_4$) and then concentrated in vacuo at 70° C. to give an oil (104 mg) which was purified by column chromatography on silica gel (2.9 g) eluted with a gradient of ethyl acetate:hexane (1:2 to 2:1). This gave the title compound as an oil (65 mg).

[0272] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.35 (m, 9H), 1.4-1.55 (n, 2H), 1.6 (n, 1H), 2.0 (m, 1H), 2.2-2.4 (n, 4H), 2.4-2.6 (m, 2H), 2.8 (n, 1H), 3.7 (s, 3H), 4.35 (d, 2H), 7.1 (d, 1H), 7.15-7.35 (m, 3H).

[0273] MS (thermospray): M/Z (MH^+) 361.4; $C_{22}H_{36}N_2O_2$+H requires 361.3.

Example 23

1-Hexyl-3,4-dimethyl-4-(3-(N-acetyl)aminomethylphenyl)-piperidine

[0274] This preparation was carried out using the procedure described for Example 22 except using acetyl chloride (35 μL, 0.49 mmol) in place of methyl chloroformate. This gave the title compound as an oil (100 mg).

[0275] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 1.95-2.05 (m, 4H), 2.2-2.4 (m, 4H), 2.472.6 (m, 2H), 2.8 (m, 1H), 4.4 (d, 2H), 7.1 (d, 1H), 7.15-7.35 (m, 3H).

[0276] MS (APCI): M/Z (MH^+) 345.3; $C_{22}H_{36}N_2O$+H requires 345.3.

Example 24

1-Hexyl-3,4-dimethyl-4-(3-(N-methanesulfonyl)aminomethylphenyl)piperidine

[0277] This preparation was carried out using the procedure described for Example 22 except using methanesulfonyl chloride (40 μL, 0.52 mmol) in place of methyl chloroformate. This gave the title compound as an oil (94mg).

[0278] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.4 (m, 4H), 2.4-2.65 (m, 2H), 2.75-2.9 (m, 4H), 4.3 (s, 2H), 7.15 (d, 1H), 7.2-7.35 (m, 3H).

[0279] MS (APCI): M/Z (MH^+) 381.6; $C_{21}H_{36}N_2O_2S$+H requires 381.3.

Example 25

1-Hexyl-3,4-dimethyl-4-(3-(N-trifluoromethanesulfonyl)-aminomethylphenyl)piperidine

[0280] To a solution of 1-hexyl-3,4-dimethyl-4-(3-aminomethylphenyl)piperidine (Example 21, 100 mg, 0.33 mmol) in pyridine (1.5 mL, dried over basic alumina) stirred under nitrogen was added trifluoromethanesulfonyl chloride (0.3 mL, 0.28 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. Aqueous sodium hydroxide (20 mL of 2) was added and the mixture was extracted with dichloromethane (3×20 mL). The aqueous layer was treated with dilute aqueous hydrochloric acid (20 mL of 1 N) and then extracted with dichloromethane (2×20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated in vacuo to give an orange oil (40 mg) which was purified by column chromatography on silica gel (1.2 g) eluted with a gradient of ethyl acetate:hexane:triethylamine (20:80: 1) to ethyl acetate triethylamine (100:1). This gave the title compound as an oil (30 mg).

[0281] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.75 (m, 6H), 2.8 (m, 1H), 4.4 (s, 2H), 7.15 (d, 1H), 7.2-7.35 (m, 3H).

[0282] MS (thermospray): M/Z (MH^+) 435.1; $C_{21}H_{33}F_3N_2O_2S$+H requires 435.2.

Example 26

1-Hexyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine

[0283] A solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 1, 1.5 g, 3.6 mmol) in 1,4-dioxan (17 mL) was de-oxygenated by evacuating and flushing with nitrogen five times. Vinyl tributyl tin (1.06 mL, 3.71 mmol) was added under stirring, followed by lithium chloride (456 mg, 10.76 mmol), tetrakis(triphenylphosphine)palladium(0) (catalytic) and 2,6-di-tert-butyl-4-methylphenol (2 crystals). The suspension was stirred under nitrogen and heated at reflux for ten hours. After cooling to room temperature the reaction mixture was quenched with aqueous ammonium hydroxide solution (50 mL, 1.0 M) and further diluted with ethyl acetate (50 mL). The phases were separated and the aqueous layer was further extracted with ethyl acetate (3×25 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (120 g) eluted with ethyl acetate:hexane:0.880 ammonia (39:60:1) to give the title compound as an oil (890 mg).

[0284] NMR ($CDCl_3$): 0.75 (d, 3H), 0.85 (m, 3H), 1.2-1.4 (m, 9H),1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 5.25 (d, 1H), 5.75 (d, 1H), 6.7 (dd, 1H), 7.1-7.35 (m, 4H).

[0285] MS (thermospray): M/Z (MH^+) 300.4; $C_{21}H_{33}N$+H requires 300.3.

Example 27

1-Hexyl-3,4-dimethyl-4-(3-(1,2-dihydroxyethyl)phenyl)-piperidine

[0286] 1-Hexyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine (Example 26, 200 mg, 0.67 mmol) was dissolved in a mixture of water (2 mL) and acetone (18 mL). 4-methylmorpholine N-oxide (172 mg, 1.47 mmol) was added with stirring followed by osmium tetroxide (200 μL, 2.5% w/w in tert-butanol). The reaction mixture was stirred at room temperature for 4 hours before the solvent was removed by evaporation in vacuo. The residue was partitioned between diciforomethane (25 mL) and water (25 mL). The organic phase was separated and dried (Na_2SO_4). Concentration in vacuo gave a residue which was purified by column chromatography on silica gel (10 g) eluted with a gradient of ethyl acetate:hexane:ammonium hydroxide solution (50:49:1 to 60:33:1), followed by ethyl acetate: methanol: ammonium hydroxide solution (94:5:1). Combination of the appropriate fractions and evaporation to dryness in vacuo gave the product as a yellow oil (145 mg).

[0287] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (n, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.05 (n, 1H), 2.2-2.45 (n, 4H), 2.45-2.65 (n, 2H), 2.8 (m, 1H), 3.7 (m, 2H), 4.80 (n, 1H), 7.1-7.4 (m, 4H).

[0288] MS (thermospray): M/Z (MH^+) 334.5; $C_{21}H_{35}NO_2$+H requires 334.3.

Example 28

1-Hexyl-3,4-dimethyl-4-(3-formylphenyl)piperidine

[0289] 1-Hexyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine (Example 26, 200 mg, 0.67 mmol) was dissolved in a mixture of water (2 μL) and acetone (18 mL). Osmium tetroxide (200 μL, 2.5% w/w in tert-butanol) was added, followed by sodium periodate (572 mg, 2.68 mmol) which was added portionwise. The reaction mixture was stirred at room temperature for 26 hours, then it was filtered to remove precipitate and the solvent was removed by evaporation in vacuo. The residue was partitioned between dichloromethane (25 mL) and saturated sodium chloride solution (25 mL). The organic phase was separated, dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel (50 g) eluted with

ethyl acetate:hexane:0.880 ammonia (74:25:1). The title compound was obtained as an oil (80 mg).

[0290] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.6 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 211), 2.85 (m, 11H), 7.5 (t, 1H), 7.55 (d, 1H), 7.7 (d, 1H), 7.8 (s, 1H), 10.0 (s, 1H).

[0291] MS (electrospray): M/Z (MH^+) 302.0; $C_{20}H_{31}NO+H$ requires 302.2.

Example 29

1-Hexyl-3,4-dimethyl-4-(3-(N-hydroxy)iminomethylphenyl)piperidine

[0292] A solution of 1-hexyl-3,4-dimethyl-4-(3-formylphenyl)piperidine (Example 28, 80 mg, 0.27 mmol) in a mixture of pyridine (1 mL) and ethanol (1 mL) was treated with hydroxylamine hydrochloride (22 mg, 0.32 mmol) and the resulting mixture was heated at reflux for 18 hours. The solvent was evaporated in vacuo and the residual orange oil was purified by column chromatography on silica gel (10 g) eluted with a gradient of dichloromethane:methanol:0.880 ammonia (98:1:1 to 94:5:1). This gave the title compound as an oil (18 mg).

[0293] NMR ($CDCl_3$, selected data): 0.8 (d, 3H), 0.85 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.6 (m, 2H), 1.7 (m, 1H), 2.1 (m, 1H), 2.2-2.75 (m, 6H), 2.95 (m, 1H), 7.2-7.4 (m, 3H), 7.6 (s, 1H), 8.1 (s, 1H).

[0294] MS (thermospray): M/Z (MH^+) 317.6; $C_{20}H_{32}N_2O+H$ requires 317.3.

Example 30

1-Hexyl-3,4-dimethyl-4-(3-acetylphenyl)piperidine

[0295] To a solution of 1-hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine (Example 1, 791 mg, 2.65 mmol) in anhydrous tetrahydrofuran (6 mL) at 0° C. was added methyl lithium (2.46 mL, 3.45 mmol) and the mixture darkened. The solution was then warmed to room temperature and stirred under a nitrogen atmosphere for 1 hour before being poured onto water (10 mL). The basic aqueous layer was extracted with diethyl ether:ethyl acetate (1:1, 3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. This gave the crude title compound as a colourless oil (720 mg, 86%).

[0296] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, .H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.6 (s, 3H), 2.85 (m, 1H), 7.4 (t, 1H), 7.5 (d, 1H), 7.75 (d, 1H), 7.95 (s, 1H).

[0297] MS (thermospray): M/Z (MH^+) 316.3; $C_{21}H_{33}NO+H$ requires 316.3.

Example 31

1-Hexyl-3,4-dimethyl-4-(3-ethynylphenyl)piperidine

[0298] A solution of 1-hexyl-3,4-dimethyl-4-{3-[2-(trimethylsilyl)ethynyl]-phenyl}piperidine (Preparation 4, 150 mg, 0.40 mmol) in tetrahydrofuran (2 mL) was cooled to -70° C. and tetrabutylammonium fluoride (1.0 M in THF, 0.41 mL, 0.41 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature gradually before being diluted with dichloromethane (10 mL) and water (10 mL). The phases were separated and the aqueous layer was further extracted with dichioromethane (2×10 mL). The combined organics were dried (Na_2SO_4) and the solvent evaporated in vacuo. The oily yellow residue was purified by column chromatography on silica gel (10 g) eluted with ethyl acetate:hexane 0.880 ammonia (10:89:1) to give the title compound as an oil (100 mg).

[0299] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.35 (m, 9H), 1.35-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.6 (m, 6H), 2.8 (m, 1H), 3.05 (s, 1H), 7.2-7.35 (m, 3H), 7.45 (s, 1H).

[0300] MS (APCI): M/Z (MH^+) 298.6; $C_{21}H_{31}N+H$ requires 298.3.

Example 32

1-Hexyl-3,4-dimethyl-4-(3-(1,1-dimethyl)hydroxymethylphenyl)piperidine

[0301] A solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine (Example 3, 50 mg, 0.15 mmol) in anhydrous tetrahydrofuran was de-oxygenated by evacuating and flushing with nitrogen three times. The solution was then cooled to 0° C. and treated with methyimagnesium chloride (0.5 mL, 1.5 mmol, 3.0 M in tetrahydrofuran) dropwise. The reaction mixture was stirred at 50° C. for 2 hours and then saturated aqueous ammonium chloride solution (20 mL) was added followed by saturated aqueous sodium hydrogencarbonate (20 mL). The mixture was extracted with ethyl acetate (3×15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give an oil (39 mg). The residue was purified by column chromatography on silica gel (1 g) eluted with a gradient of ethyl acetate:hexane:ammonia (50:50:1 to 25:75:1) to give the title compound as a colourless oil (30 mg).

[0302] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.25-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (s, 61H), 1.65 (m, 1H), 2.05 (m, 11H), 2.2-2.45 (m, 41H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 7.15 (m, 1H), 7.2-7.3 (m, 2H), 7.45 (s, 1H).

[0303] MS (APCI): M/Z (MH^+) 332.4; $C_{22}H_{37}NO+H$ requires 332.3.

Example 33

1-Hexyl-3,4-dimethyl-4-(3-hydroxymethylphenyl)-piperidine

[0304] A stirred solution of 1-hexanoyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Preparation 7, 80 mg, 0.23 mmol) in anhydrous tetrahydrofuran (1 mL) under nitrogen was treated with lithium aluminium hydride (1.0 M in ether, 0.70 mL, 0.70 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was then quenched with water (7.5 mL) and extracted with ethyl acetate (7 mL). The phases were separated and the aqueous layer was further extracted with ethyl acetate (2×5 mL). The combined organics were dried (Na_2SO_4) and the solvent removed in vacuo to give the title compound as a pale oil (30 mg).

[0305] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0

(m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1M, 4.7 (s, 21), 7.1-7.35 (m, 41H).

[0306] MS (thermospray): M/Z (MH^+) 304.3; $C_{20}H_{33}NO+H$ requires 304.3.

Example 34

1-Hexyl-3,4-dimethyl-4-(3-(2-hydroxyethyl)phenyl)-piperidine

[0307] To a stirred solution of 1-hexanoyl-3,4-dimethyl-4-(3-vinylphenyl)-piperidine (Preparation 8, 50 mg, 0.16 mmol) in bis(2-methoxyethyl)ether (1.5 mL) at 0° C. under nitrogen was added dropwise borane (1.0 M in tetrahydrofuran, 0.35 mL, 0.35 mmol). The reaction mixture was stirred at 0° C. for 30 minutes and then for 2 hours at room temperature. Trimethylamine N-oxide (48 mg, 0.64 mmol) was subsequently added and the reaction mixture heated at reflux under a nitrogen atmosphere for 2 hours. To the cooled reaction was then added diethyl ether (10 mL) and saturated aqueous sodium chloride solution (10 mL). The phases were separated and the aqueous layer was further extracted with diethyl ether (10 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1.5 g) eluted with ethyl acetate:hexane (50:50) to give the title compound as an oil (30 mg).

[0308] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (m, 3H), 1.25-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 2.85 (t, 2H), 3.85 (t, 2H), 7.05 (d, 1H), 7.1-7.35 (m, 3H).

[0309] MS (APCI): M/Z (MH^+) 318.6; $C_{21}H_{35}NO+H$ requires 318.3.

Example 35

1-Hexyl-3,4-dimethyl-4-(3-(1-hydroxy-2-methy-lamino)-ethylphenyl)piperidine

[0310] To a solution of 1-hexanoyl-3,4-dimethyl-4-{3-[4-(4-methylphenyl)-sulfonyl-4,5-dihydro-1,3-oxazol-5-yl] phenyl}piperidine (Preparation 10, 345 mg, 0.68 mmol) in anhydrous tetrahydrofuran (5 mL) at room temperature was added lithium aluminium hydride (1.0 M solution in tetrahydrofuran, 0.74 mL, 0.74 mmol) dropwise over five minutes. The solution was stirred at room temperature under a nitrogen atmosphere for 2 hours and then cooled to 0° C. The reaction was quenched cautiously by the addition of aqueous sodium hydroxide solution (1.0 mL, 1.0 N) and then ethyl acetate (20 mL) and solid sodium hydrogencarbonate (excess) were added. The mixture was stirred vigorously for 30 minutes and then filtered through Celite®, washing with ethyl acetate. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel eluted with neat ethyl acetate and then ethyl acetate-:methanol:0.880 ammonia (70:30:1) to give the title compound as a clear gum (120 mg).

[0311] NMR ($CDCl_3$, selected data): 0.75 (d, 3H), 0.9 (t, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.6 (m, 9H), 2.65-2.85 (m, 3H), 4.75 (m, 1H), 7.1-7.35 (m, 4H).

[0312] MS (thermospray): M/Z (MH^+) 347.3; $C_{22}H_{38}N_2O+H$ requires 347.3.

[0313] Preparation of Starting Materials

[0314] Preparation 1: 1-Hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine

[0315] To a solution of 1-hexyl-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (3.5 g, 12 mmol, *J. Med. Chem.*, 1993, 36, 2833) in dichloromethane (15 mL) was added triethylamine (3 mL) followed by N-phenyltrifluoromethanesulfonimide(6.1 g, 18 mmol) portionwise. The reaction mixture was stirred under nitrogen at room temperature for 18 hours then it was washed with aqueous sodium hydroxide solution (60 mL of 2 N). The separated aqueous layer was back-washed with dichloromethane (2×30 mL), after which the combined organics were dried (Na_2SO_4) and the solvent removed in vacuo to give a yellow oil. This was purified by column chromatography on silica gel (150 g) eluted with hexane:ethyl acetate:0.880 ammonia (66:33:1) to give the title compound as a yellow oil (4.22 g).

[0316] NMR ($CDCl_3$): 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.7 (m, 3H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 7.1 (d, 1H), 7.15 (s, 1H), 7.25-7.45 (m, 2H).

[0317] MS (thermospray): M/Z (MH^+) 422.3; $C_{20}H_{30}F_3NO_3S+H$ requires 422.2.

[0318] Preparation 2: 1-Benzyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine

[0319] To a stirred solution of 1-benzyl-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (10.16 g, 34.4 mmol, *J. Med. Chem.*, 1993, 36, 2833) in anhydrous dichloromethane (100 mL) was added triethylamine (8 mL) and the resulting solution was de-oxygenated by evacuating and flushing with nitrogen three times. N-Phenyltrifluoromethanesulfonimide (18.43 g, 51.6 mmol) was added and the mixture was de-oxygenated again, using the same procedure as before, and stirred overnight at room temperature under nitrogen. The reaction mixture was then diluted with dichloromethane (200 mL) and washed with aqueous sodium hydroxide solution (200 mL of 1 M). The aqueous phase was back-washed with dichloromethane (2×100 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo to give an orange oil (ca 20 g) which was purified by column chromatography on silica gel (700 g) eluted with a gradient of ethyl acetate:hexane:0.880 ammonia (10:190:1 to 10:90:1). This gave the title compound as a colourless oil (13.98 g). NMR ($CDCl_3$): 0.75 (d, 3H), 1.35 (s, 3H), 1.55 (m, 1H), 1.95 (m, 1H), 2.25-2.5 (m, 2H), 2.5-2.65 (m, 2H), 2.85 (m, 1H), 3.45 (d, 1H), 3.6 (d, 1H), 7.1 (d, 1H), 7.15 (s, 1H), 7.2-7.45 (m, 7H).

[0320] MS (thermospray): M/Z (MH^+) 428.0; $C_{21}H_{24}F_3NO_3S+H$ requires 428.2.

[0321] Preparation 3: 3,4-Dimethyl-4-(3-(N-ethyl)amidophenyl) piperidine

[0322] To a solution of 1-benzyl-3,4-dimethyl-4-(3-(N-ethyl)amidophenyl)-piperidine (Example 16, 800 mg, 2.3 mmol) in methanol (40 mL) was added palladium on activated carbon (150 mg, Degussa type E101 NE/W, Pd 10% dry weight, ca 50% water). The resulting suspension was stirred at room temperature under an atmosphere of hydrogen at 415 kPa for 1½ days. It was then filtered through Celite® to remove the catalyst residues and concentrated in vacuo to give a foam (610 mg). Purification by column

chromatography on silica gel (30 g) eluted with CH_2Cl_2:EtOH 0.880 ammonia (50:8:1) gave the title compound as a thick gum (557 mg).

[0323] NMR ($CDCl_3$, selected data): 0.7 (d, 3H),1.25 (t, 3H), 1.4 (s, 3H), 1.95 (m, 1H), 2.15 (m, 1H), 2.75 (m, 1H), 2.95-3.15 (m, 2H), 3.25 (m, 1H), 3.5 (m, 2H), 7.3-7.45 (m, 2H), 7.5 (d, 1H), 7.7 (s, 1H).

[0324] MS (APCI): M/Z (MH^+) 261.5; $C_{16}H_{24}N_2O$+H requires 261.2.

[0325] Preparation 4: 1-Hexyl-3,4-dimethyl-4-{3-[2-(trimethylsilyl)ethynyl]-phenyl}piperidine

[0326] To a solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 1, 350 mg, 0.83 mmol) in tetrahydrofuran (12 mL) was added diisopropylamine (4 mL) and trimethylsilylethyne (4.5 g, 46 mmol) and the mixture was de-oxygenated by evacuating and flushing with nitrogen five times. Copper(I) iodide (6.2 mg 0.033 mmol), and then catalytic quantities of palladium(II) acetate and 1,1 '-bis(diphenylphosphino)ferrocene were added. The reaction mixture was heated to reflux under nitrogen for 8 hours, before being allowed to cool to room temperature. Water (10 mL) and dichloromethane (10 mL) were added, the phases separated and the aqueous layer further extracted with dichloromethane (2×10 mL). The combined organics were then dried (Na_2SO_4) and the solvent removed in vacuo. The residual brown oil was purified by column chromatography on silica gel (25 g) eluted with a gradient of ethyl acetate:hexane:0.880 ammonia (20:79:1 to 50:49:1) to give the title compound as an oil (150 mg).

[0327] NMR ($CDCl_3$): 0.25 (s, 9H), 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.4 (m, 4H), 2.4-2.6 (m, 2H), 2.8 (m, 1H), 7.2-7.35 (m, 3H), 7.4 (s, 1H).

[0328] MS (thermospray): M/Z (MH^+) 370.4; $C_{24}H_{39}NSi$+H requires 370.3.

[0329] Preparation 5: 1-Hexanoyl-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine

[0330] To a stirred solution of 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (3.8 g, 18.6 mmol, *J. Org. Chem.*, 1991, 56, 1660) in dichloromethane (30 mL) at 0° C. was added triethylamine (3.9 mL, 27.8 mmol) followed by the dropwise addition of hexanoic anhydride (4.7 mL, 20.4 mmol) over 5 minutes. The reaction was stirred under a nitrogen atmosphere for 3 hours at room temperature and then quenched by the addition of saturated aqueous sodium hydrogencarbonate (50 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate:hexane (1:1). The title compound was obtained as a clear oil (4.5 g).

[0331] NMR ($CDCl_3$, selected data from a 13:9 mixture of rotamers): 0.65 (d, 3H), 0.9 (m, 3H), 1.25-1.45 (m, 7H), 1.55-1.75 (m, 3H), 2.05 (m, 1H), 2.15 (m, 1H), 2.25-2.55 (m, 2H), 2.95 (m, 0.59H), 3.15 (m, 0.41H), 3.35 (m, 0.41H), 3.5-3.7 (m, 1.18H), 3.85 (m, 0.41H), 4.4 (m, 0.41H), 4.75 (m, 0.59H), 6.7 (d, 1H), 6.75-6.85 (m, 2H), 7.15 (t, 1H).

[0332] MS (thermospray): M/Z (MH^+) 304.1; $C_{19}H_{29}NO_2$+H requires 304.2.

[0333] Preparation 6: 1-Hexanoyl-3,4-dimethyl-4-(trifluoromethanesulfonyloxyphenyl)piperidine

[0334] To a stirred solution of 1-hexanoyl-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (Preparation 5, 3.1 g, 10.1 mmol) in dichloromethane (30 mL) at room temperature was added triethylainine (2.82 mL, 20.2 mmol) followed by N-phenyltrifluoromethanesulfonimide (3.6 g, 15.1 mmol) portionwise. The reaction was stirred under a nitrogen atmosphere at room temperature for 16 hours and then aqueous sodium hydroxide (30 mL of 2 N) was added. The bi-phasic mixture was stirred vigorously for 2 hours before the two layers were separated and the aqueous layer extracted with dichloromethane (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a gradient of ethyl acetate:hexane (1:2 and then 2:1). The title compound was obtained as a clear oil (3.6 g).

[0335] NMR ($CDCl_3$, selected data from a 7:5 mixture of rotamers): 0.55-0.65 (m, 3H), 0.85-0.95.(m, 3H), 1.25-1.4 (m, 4H), 1.45 (s, 3H), 1.55-1.75 (m, 3H), 2.0-2.5 (m, 4H), 2.9 (m, 0.58H), 3.15 (m, 0.42H), 3.35 (m, 0.42H), 3.6 (m, 1.16H), 3.9 (m, 0.42H), 4.4 (m, 0.42H), 4.75 (m, 0.58H), 7.05-7.15 (m, 2H), 7.3 (m, 1H), 7.4 (m, 1H).

[0336] MS (thermospray): M/Z (MH^+) 436.4; $C_{20}H_{28}F_3NO_4S$+H requires 436.2.

[0337] Preparation 7: 1-Hexanoyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine

[0338] To a solution of 1-hexanoyl-3,4-dimethyl-4-(trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 6, 267 mg, 0.48 mmol) in anhydrous N,N-dimethylformamide (2 mL) was added triethylamine (0.18 mL) and methanol (0.4 mL). The mixture was de-oxygenated by evacuating and flushing with nitrogen five times. Palladium(II) acetate (4.4 mg) and 1,1'-bis(diphenylphosphino)ferrocene (8 mg) were added and the solution was purged with carbon monoxide. The reaction mixture was heated to 60° C. under an atmosphere of carbon monoxide for 7 hours then it was cooled to room temperature and diluted with saturated aqueous sodium chloride solution (10 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (4×15 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (50 g) eluted with hexane:ethyl acetate:0.880 ammonia (66:33:1). The title compound was obtained as a pale yellow oil (110 mg).

[0339] NMR ($CDCl_3$, selected data from a 9:7 mixture of rotamers): 0.55-0.7 (m, 3H), 0.85-0.95.(m, 3H), 1.25-1.4 (m, 4H), 1.45 (s, 3H), 1.6-1.8 (m, 3H), 2.05-2.45 (m, 4H), 2.9 (m, 0.56H), 3.15 (m, 0.44H), 3.4 (m, 0.44H), 3.6 (m, 1.12H), 3.9 (m, 0.44H), 3.95 (s, 3H), 4.4 (0.44H), 4.7 (m, 0.56H), 7.35-7.5 (m, 2H), 7.9 (m, 1H), 7.95 (m, 1H).

[0340] MS (thermospray): M/Z (MH^+) 346.3; $C_{21}H_{31}NO_3$+H requires 346.2.

[0341] Preparation 8: 1-Hexanoyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine

[0342] To a stirred solution of 1-hexanoyl-3,4-dimethyl-4-(trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 6, 3.0 g, 6.90 mmol) in tetrahydrofuran (30 mL) at room temperature were added sequentially vinyltributyltin (2.12 mL, 7.24 mmol), lithium chloride (585 mg, 13.8 mmol), and tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.69 mmol). The mixture was heated to reflux under a nitrogen atmosphere for 1½ hours at which time a few crystals of 4-tert-butylcatechol were added. Heating at reflux was then continued for a further 16 hours. The mixture was cooled and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a gradient of ethyl acetate:hexane (1:10 to 1:3). The title compound was obtained as a clear oil (2.1 g).

[0343] NMR ($CDCl_3$, selected data from a 5:4 mixture of rotamers): 0.55-0.7 (m, 3H), 0.85-1.0 (m, 3H), 1.25-1.4 (m, 4H), 1.4 (s, 3H), 1.6-1.75 (m, 3H), 2.05-2.45 (m, 4H), 2.9 (m, 0.56H), 3.15 (m, 0.44H), 3.35 (m, 0.44H), 3.6 (m, 1.12H), 3.9 (m, 0.44H), 4.4 (m, 0.44H), 4.7 (m, 0.56H), 5.25 (d, 1H), 5.75 (d, 1H), 6.7 (dd, 1H), 7.15 (m, 1H), 7.2-7.35 (m, 31H).

[0344] MS (APCI): M/Z (MH^+) 314.5; $C_{21}H_{31}NO$+H requires 314.2.

[0345] Preparation 9: 1-Hexanoyl-3,4-dimethyl-4-(3-formylphenyl)piperidine

[0346] To a solution of 1-hexanoyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine (Preparation 8, 2.4 g, 7.67 mmol) in acetone (20 mL) at room temperature was added water (5 mL), 4-methylmorpholine N-oxide (1.1 g, 9.20 mmol) and finally osmium tetroxide (3.83 mL, 2.5 wt % solution in tert-butanol). The yellow solution was stirred at room temperature for 1 hour and then sodium periodate (4.92 g, 23.0 mmol) was added in one portion. After stirring the reaction for 3 hours a heavy precipitate had developed and the reaction mixture was filtered through Celite®, washing with acetone. The filtrate was concentrated in vacuo, the crude oil was dissolved in dichloromethane, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate:hexane (1:1). The title compound was isolated as clear oil (2.0 g).

[0347] NMR ($CDCl_3$, selected data from a 1:1 mixture of rotamers): 0.55-0.7 (m, 3H), 0.85-0.95 (m, 3H), 1.25-1.4 (m, 4H), 1.45 (s, 3H), 1.55-1.8 (m, 3H), 2.1-2.5 (m, 4H), 2.95 (m, 0.5H), 3.15 (m, 0.5H), 3.4 (m, 0.5H), 3.6 (m, 1H), 3.9 (m, 0.5H), 4.4 (m, 0.5H), 4.75 (m, 0.5H), 7.45-7.6 (m, 2H), 7.7 (m, 1H), 7.75 (m, 11H), 10.0 (s, 1H).

[0348] MS (thermospray): M/Z (MH^+) 316.3; $C_{20}H_{29}NO_2$+H requires 316.2.

[0349] Preparation 10: 1-Hexanoyl-3,4-dimethyl-4-{3-[4-(4-methylphenyl)-sulfonyl-4,5-dihydro-1,3-oxazol-5-yl] phenyl}piperidine

[0350] To a solution of 1-hexanoyl-3,4-dimethyl-4-(3-formylphenyl)piperidine (Preparation 9, 758 mg, 2.40 mmol) in ethanol (20 mL) was added [(4-methylphenyl)sulfonyl]methyl isocyanide (460 mg, 2.34 mmol) followed by sodium cyanide (12 mg, 0.24 mmol). The mixture was stirred at room temperature under a nitrogen atmosphere for five hours and then concentrated in vacuo. The residue was purified by column chromatography on silica gel using a gradient elution of hexane:ethyl acetate (67:33 to 0:100). The title compound was isolated as a clear oil (909 mg).

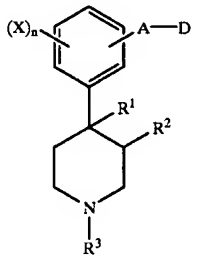
[0351] NMR ($CDCl_3$) (selected data from a 1:1 mixture of rotamers): 0.55-0.65 (m, 3H), 0.85-0.95 (m, 3H), 1.25-1.45 (m, 7H), 1.55-1.75 (m, 3H), 2.05-2.45 (m, 4H), 2.45 (s, 3H), 2.9 (m, 0.51H), 3.15 (m, 0.5H), 3.35 (m, 0.5H), 3.6 (m, 11H), 3.9 (m, 0.51H), 4.4 (m, 0.51H), 4.7 (m, 0.51H), 5.0 (d, 1H), 6.05 (d, 1H), 7.1-7.3 (m, 41H), 7.3-7.45 (m, 31H), 7.85 (d, 2H).

[0352] MS (thermospray) M/Z (MH^+) 511.1; $C_{29}H_{38}N_2O_4S$+H requires 511.3.

[0353] Biological Activity

[0354] The Ki values of certain compounds of the present invention in the opioid receptor binding assays were determined, and the compounds of Examples 4, 8, 18 and 20 were all found to have Ki values of 4000 nM or less for the μ receptor. The compounds of the invention also possess affinity at the δ and κ opioid receptors.

1. A compound of formula I,



I

wherein

A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH;

D represents H, OH, CN, $N(R^4)(R^5)$, $N(H)R^6$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, C(O)RS, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$;

provided that when A represents C_{2-4} alkenylene or C_{2-4} alkynylene, and D represents OH, $N(R^4)(R^5)$ or $N(H)R^6$, then D is not directly attached to an unsaturated carbon atom;

and provided that when A represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$;

R^4 and R^5 independently represent H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^4 and R^5,

together with the N-atom to which they are attached, form a 4- to 7-membered heterocyclic ring, which ring optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur and which ring is optionally substituted by one or more substituents selected from C_{1-4}, alkyl, C_{1-4} alkoxy, OH, =O, nitro, amino or halo;

R^6 represents $C(O)R^{10a}$, $C(O)OR^{10b}$ or $S(O)_2R^{10c}$;

R^{10a} to R^{10c} independently represent C_{1-4} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl (which four groups are all optionally substituted by or one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), or R^{10a} represents H;

R^7 and R^8 independently represent H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

R^{9a} and R^{9b} independently represent C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^{9b} represents H;

R^1 and R^2 are each independently H or C_{1-4} alkyl;

R^3 represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and $—N(R^{11a})(R^{11b})$, C_{1-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{12a})S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $—W—A^1—N(R^{12b})(R^{12c})$;

p is 0, 1 or 2;

W represents a single bond, C(O) or $S(O)_q$;

A^1 represents a single bond or C_{1-10} alkylene;

provided that when both W and A^1 represent single bonds, then the group $—N(R^{12b})(R^{12c})$ is not directly attached to an unsaturated carbon atom;

q is 0, 1 or 2;

R^{11a} to R^{11d} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)) or Het^2;

provided that R^{11d} does not represent H when p represents 1 or 2;

R^{11a} to R^{12c} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het^3, or R^{12b} and R^{12c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally interrupted by O, S and/or an $N(R^{14})$ group and is optionally substituted by one or more C_{1-4} alkyl groups;

R^{13} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents selected from C_{1-4} alkyl, C_{1-4}alkoxy, OH, nitro, amino or halo;

R^{14} represents H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $A^2—(C_{3-8}$ cycloalkyl) or A^2-aryl;

A^2 represents C_{1-6} alkylene;

Het^1, Het^2 and Het^3 independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);

X is H, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

n is 0, 1 or 2;

or pharmaceutically, or veterinarily, acceptable derivatives thereof.

2. A compound as claimed in claim 1 wherein the group A-D is attached in the meta-position relative to the piperidine ring.

3. A compound as claimed in claim 1 or claim 2 wherein R^1 represents C_{1-2} alkyl.

4. A compound as claimed in any one of claims 1 to 3 wherein R^2 represents H or C_{1-2} alkyl.

5. A compound as claimed in any one of claims 1 to 4 wherein R^3 represents saturated C_{1-10} alkyl, optionally substituted by one or more substituents selected from OR^{11c}, CN, halo, C_{2-4} alkanoyl, C_{1-4} alkoxy carbonyl, $N(R^{12a})SO_2R^{13}$, Het^1, aryl (which latter group is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$), or $—W—A^1—N(R^{12b})(R^{12c})$.

6. A compound as claimed in any one of claims 1 to 5 wherein R^{11c} represents H, C_{1-6} alkyl or aryl (which latter groups is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$); R^{12a} to R^{12c} independently represent H, C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which latter three groups are optionally substituted by one

or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy); W represents C(O); and/or A^1 represents a single bond.

7. A compound as claimed in any one of claims 1 to 6 wherein R^{13} represents C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which three groups are all optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy).

8. A compound as claimed in any one of claims 1 to 7 wherein A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more OH and/or methyl groups.

9. A compound as claimed in any one of claims 1 to 8 wherein D represents H, OH, CN, $N(H)R^4$, $N(H)C(O)R^{10a}$, $N(H)C(O)OR^{10b}$, $N(H)S(O)_2R^{10c}$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$ or $C(=NOH)R^8$; R^4 and R^5 independently represent H, C_{1-4} alkyl or C_{1-3} alkylphenyl, which latter two groups are optionally substituted by C_{1-4} alkoxy; R^7 and R^8 independently represent H or C_{1-4} alkyl; and/or R^{10a} to R^{10c} independently represent C_{1-4} alkyl, which group is optionally substituted by one or more halo atoms.

10. A compound as claimed in any one of claims 1 to 9 wherein R^3 represents saturated C_{1-7} alkyl, optionally substituted by one or more substituents selected from CN, O—(C_{1-4} alkyl), phenyl, or O-(phenyl).

11. A compound as claimed in any one of claims 1 to 10 wherein X represents halo.

12. A compound as claimed in any one of claims 1 to 11 wherein n represents 0 or 1.

13. A compound as defined in any one of claims 1 to 12, for use as a medicament.

14. A compound as defined in any one of claims 1 to 12, for use as an animal medicament.

15. A formulation comprising a compound as defined in any one of claims 1 to 12, in admixture with a pharmaceutically, or a veterinarily, acceptable adjuvant, diluent or carrier.

16. A formulation as claimed in claim 15, which is a veterinary formulation.

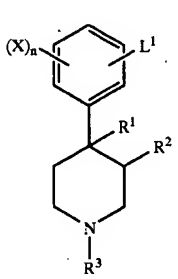
17. The use of a compound as defined in any one of claims 1 to 12, in the manufacture of a medicament for the curative or prophylactic treatment of a disease mediated via an opiate receptor.

18. The use as claimed in claim 17, wherein the disease is pruritus.

19. A method of treating or preventing a disease mediated by an opiate receptor, which comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 12, to a patient in need of such treatment.

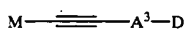
20. A process for the preparation of a compound as defined in claim 1, which comprises:

a) for compounds of formula I in which A represents C_{2-4} alkynylene (in which group the carbon-carbon triple bond is α,β to the benzene ring), which alkynylene group is optionally substituted at the 3- and/or the 4-C (relative to the benzene ring) by one or more substituents defined in claim 1 in respect of A, and/or one of the groups defined in claim 1 in respect of D, or (when D is not attached at the 3- or 4-C) which alkynylene group is substituted at the 2-C (relative to the benzene ring) by CN, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, reaction of a corresponding compound of formula II,



II

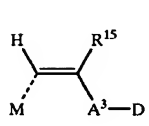
wherein L^1 is a leaving group, and R^1, R^2, R^3, X and n are as defined in claim 1, with a compound of formula III,



III

wherein M represents (as appropriate) H, a tin-containing moiety, a boron derivative, a zinc halide, a magnesium halide or an alkali metal, A^3 represents a single bond or C_{1-2} alkylene (optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH or halo), and D is as defined in claim 1, provided that when A^3 represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$, wherein R^4, R^5 and R^6 are as defined in claim 1;

b) for compounds of formula I in which A represents C_{2-4} alkenylene (in which group the carbon-carbon double bond is α,β to the benzene ring), which alkenylene group is optionally substituted at the 2-C (relative to the benzene ring) by C_{1-4} alkyl, and also optionally substituted at the 3- and/or 4-C (relative to the benzene ring) by one or more of the substituents defined in claim 1 in respect of A and/or one of the groups defined in claim 1 in respect of D, or which alkenylene group is substituted at the 2-C (relative to the benzene ring) by CN, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, reaction of a corresponding compound of formula II, as defined above, with a compound of formula

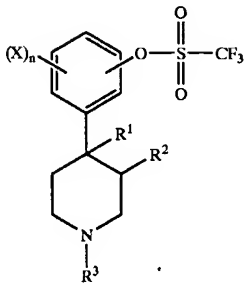


IV

wherein the dashed bond represent optional cis- or trans-geometry, R^{15} represents H or C_{1-4} alkyl, A^3 and M are as defined above, and D is as defined in claim 1;

c) for compounds of formula I in which A represents a single bond and D represents CN, reaction of a compound of formula V,

V



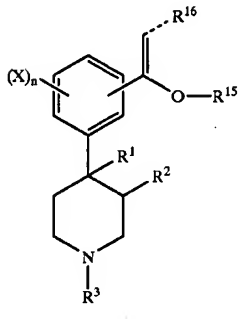
wherein R^1, R^2, R^3, X and n are as defined in claim 1, with an alkali metal cyanide;

d) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents NH_2 (which is attached to a CH_2 group), reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents CN;

e) for compounds of formula I in which D represents $C(O)NH_2$, controlled hydrolysis of a corresponding compound of formula I in which D represents CN;

f) for compounds of formula I in which A represents a single bond and D represents C(O)—(C_{1-6} alkyl) or C(O)—(C_{1-4} alkylphenyl), which alkyl and alkylphenyl groups are both optionally substituted by one or more of the substituents defied in claim 1 in respect of R^8, hydrolysis of a corresponding compound of formula IX,

IX



wherein R^{15} represents C_{1-6} alkyl, R^{16} represents H, C_{1-5} alkyl, phenyl or C_{1-3} alkylphenyl which latter three groups are all optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), the dashed bond indicates optional cis- or trans-geometry, and R^1, R^2, R^3, X and n are as defined in claim 1;

g) for compounds of formula I in which D represents $C(O)R^8$, wherein R^8 is as defined in claim 1 provided that it does not represent H, reaction of a corresponding compound of formula I in which D represents CN with an organometallic compound capable of delivering an R^{8a}-containing anion, wherein R^{8a} is defined as for R^8 in claim 1 provided that it does not represent H;

h) for compounds of formula I in which A represents a single bond and D represents $C(O)OR^7$, wherein R^7 is as defined in claim 1 provided that it does not represent H, reaction of a corresponding compound of formula V, as defined above, with carbon monoxide and an alcohol of formula $R^{7a}OH$, wherein R^{7a} is defined as for R^7 in claim 1 provided that it does not represent H;

i) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH (which is attached to a CH_2 group), reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above;

j) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are gem-disubstituted with two C_{1-4} alkyl groups (a to D) and are optionally substituted by one or more further substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH, reaction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above, with a C_{1-4} alkyl-delivering organometallic compound;

k) for compounds of formula I in which D represents $C(O)N(R^4)(R^5)$, wherein R^4 and R^5 are as defined in claim 1:

A) reaction of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above, with a compound of formula XI,

$HN(R^4)(R^5)$ XI

or an acid addition salt thereof, wherein R^4 and R^5 are as defined in claim 1;

B) reaction of a corresponding compound of formula I in which D represents C(O)OH with a compound of formula XI, as defined above.

l) for compounds of formula I in which D represents C(O)OH, hydrolysis of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above;

m) for compounds of formula I in which D represents $N(H)R^6$, wherein R^6 is as defined in claim 1, reaction of a corresponding compound of formula I in which D represents NH_2 with a compound of formula XII,

$$R^6—L^1 \qquad XII$$

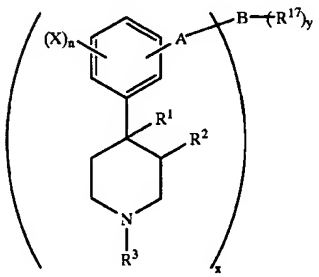
wherein R^6 is as defined in claim 1 and L^1 is as defined above; n) for compounds of formula I in which A represents C_{1-4} alkyl and D represents $N(R^4)(R^5)$ or $N(H)C(O)R^{10a}$ attached at the 1-, 2- or 3-C (relative to the benzene ring), wherein R^4, R^5 and R^{10a} are as defined in claim 1, reaction of a corresponding compound of formula I in which A represents C_{1-4} alkenylene unsaturated α,β-, β,γ- or γ,δ- (respectively) relative to the benzene ring and D represents H, with a compound of formula XI, as defined above, or a compound of formula XIII,

$$NC—R^{10a} \qquad XIII$$

wherein R^{10a} is as defined in claim 1;

o) for compounds of formula I in which A represents C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH, oxidation of a corresponding borane adduct of formula XIV,

XIV



wherein x is 1, 2 or 3, y is (as appropriate) (3-x) or 1, R^{17} is (as appropriate) H, halo, an alkyl, or a cycloalkyl group providing one or two bonds to boron, A represents (as appropriate) C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and R^1, R^2, R^3, X and n are as defined in claim 1;

p) for compounds of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH, reaction of a corresponding compound of formula I in which A represents a C_{2-4} alkenylene group and D represents H with a dihydroxylating reagent;

q) for compounds of formula I in which A represents a single bond or a C_{1-2} alkylene group (as appropriate) and D represents C(O)H, reaction of a corresponding of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH with a reagent that effects 1,2diol oxidative cleavage;

r) for compounds of formula I in which D represents $C(=NR^{9a})R^8$ or $C(=NOR^{9b})R^8$, wherein R^8, R^{9a} and R^{9b} are as defined in claim 1, reaction of a corresponding compound of formula I in which D represents $C(O)R^8$ with a compound of formula XV,

$$H_2N—R^{9a} \qquad XV$$

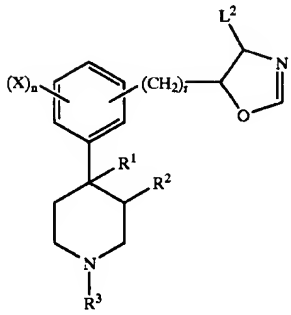
or a compound of formula XVI,

$$H_2N—OR^{9b} \qquad XVI$$

wherein R^{9a} and R^{9b} are as defined in claim 1;

s) for compounds of formula I in which A represents C_{1-4} alkylene substituted (α to D) with an OH group and D represents $N(H)CH_3$ (at the alkylene chain terminus), reduction of a corresponding compound of formula XVII,

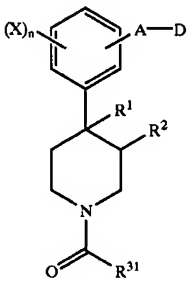
XVII



wherein r is 0, 1 or 2, L^2 represents H or a group capable, when attached to a C_2 alkylene unit, of undergoing 1,2-elimination (relative to L^2), and R^1, R^2, R^3, k and n are as defined in claim 1;

t) for compounds of formula I wherein R^3 represents C, alkyl optionally substituted by C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified in claim 1 in respect to R^3), which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom via a CH_2 group, wherein Het^1 is as defined in claim 1, reduction of a corresponding compound of formula XIX,

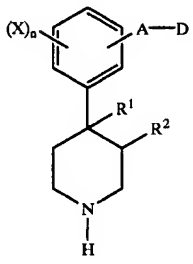
XIX



wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{12a})S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or —W—A^1—$N(R^{12b})(R^{12c})$, and R^1, R^2, R^{11c}, R^{11d}, R^{12a} to R^{12c}, $R^{13}Het^1$, n, p, W, X, A^1, A and D are as defined in claim 1;

u) reaction of a corresponding compound of formula XX,

XX



wherein R^1, R^2, A, D, X and n are as defined in claim 1, with a compound of formula VIII,

R^3—L^1 VIII

wherein R^3 is as defined in claim 1 and L^1 is as defined above;

v) for compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined in claim 1, is instead optionally substituted by R^{31}, wherein R^{31} is as defined above, reaction of a corresponding compound of formula XX, as defined above, with a compound of formula XXII,

$R^{31}CHO$ XXII

wherein R^{31} is as defined above, in the presence of a reducing agent;

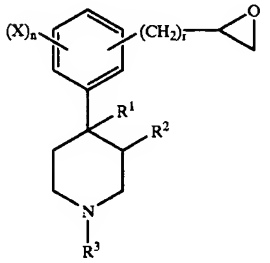
w) for compounds of formula I wherein R^3, is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, —C(O)—A^1—$N(R^{12b})(R^{12c})$, —S(O)—A^1—$N(R^{12b})(R^{12c})$, or —$S(O)_2$—A^1—$N(R^{12b})(R^{12c})$, wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as defined in claim 1, reaction of a corresponding compound of formula XX, as defined above, with a compound of formula XXIII,

R^{3a}—Z XXIII

wherein R^{3a} represents R^3 as defined in claim 1 except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, —C(O)—A^1—$N(R^{12b})(R^{12c})$—S(O)—A^1—$N(R^{12b})(R^{12c})$, or —$S(O)_2$—A^1—$N(R^{12b})(R^{12c})$, wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as defined in claim 1;

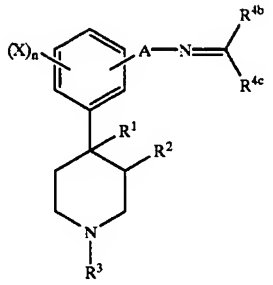
x) for compounds of formula I in which A represents C_{2-4} alkylene substituted (α to D) with an OH group and D represents $N(R^4)(R^5)$ (at the alkylene chain terminus), and R^4 and R^5 are as defined in claim 1, reaction of a compound of formula XXIV,

XXIV



wherein R^1, R^2, R^3, X and n are as defined in claim 1 and r is as defined above, with a compound of formula XI, as defined above;

y) for compounds of formula I in which D represents $N(H)R^4$, wherein R^4 is as defined in claim 1 provided that it does not represent aryl, reduction of a corresponding compound of formula XXV,



XXV

wherein R^{4b} and R^{4c}, together with the carbonyl group to which they are attached, form a C_{1-6} alkanal, C_{3-6} alkanone, C_{3-8} cycloalkanone, phenyl(C_{1-4})alkanal or phenyl(C_{2-4})alkanone group, which five groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), and R^1, R^2, R^3, A, X and n are as defined in claim 1 (provided that the $—N=C(R^{4b})(R^{4c})$ group is not directly attached to an unsaturated carbon atom);

z) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $N(^4)(R^5)$ (attached to a CH_2 group), wherein R^4 and R^5 are as defined in claim 1, reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)N(R^4)(R^5)$;

aa) conversion of one functional group on an alkyl, heterocyclic or aryl group in a compound of formula I to another.

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